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AUGUST, 1935

ORIGINAL ARTICLES.

THE PITUITARY IN EXPERIMENTAL CRETINISM.

I. STRUCTURAL CHANGES IN THE PITUITARIES OF THYROIDECTOMIZED RATS.*†

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VERY little attention has been paid to the histologic changes in the pituitary in hypothyroidism. The studies which have been published (chiefly in the German literature) show great variation in statement of observations and no agreement in interpretations of these observations. These discrepancies are probably due partly to confusion between acidophils and basophils, which Bailey and Davidoff[2] and Biedermann[3] have shown may easily occur by various staining techniques, and due partly to previous lack of knowledge of the facts that are now established concerning the concrete functions of the pituitary cells. The present study was made with the view of studying the pituitary after thyroidectomy in the light of our recently acquired knowledge of the definite thyroid-pituitary relationship.

* Presented before the Philadelphia Pathological Society, February 14, 1935.

† Aided in part by a grant from the Faculty Research Committee of the University of Pennsylvania.

At present the growth hormone of the pituitary is attributed to the acidophil (or eosinophil) cells which in the rat constitute roughly 32% of the cells, and the gonadotropic hormones to the basophil cells which constitute about 15% of the cells.[15] The acidophils and basophils are called chromophils because their granules take up dyes. The poorly staining chromophobes or chief cells, whose activities are unknown, make up the remaining 53% of the cells. Severinghaus[15] gives a good discussion of the various points of view concerning possible transitions of one cell type to another.

The existence of thyrotropic hormone has been demonstrated by pituitary implants and extracts, which produce definite structural changes of hyperplasia in the thyroid and raise the basal metabolic rate, the guinea pig being particularly sensitive for its demonstration. No one has so far ventured to ascribe the production of this hormone to any of the cell types in the pituitary. Removal of the pituitary results in atrophy of the thyroid and decreased basal metabolic rate which is ascribed to absence of the thyrotropic hormone.

The present paper is concerned with the structural changes in the pituitary resulting from the loss of thyroid secretion.

Experimental Methods. The white rats used were in most instances litter mates, in a few cases rats of the same age but of different litters. Thyroids were removed under ether anesthesia, avoiding the parathyroids, and growth curves plotted thereafter. The operation was carried out at ages varying from 24 to 69 days (average 41 days). The stunting of growth was taken as the criterion for adequate thyroidectomy. Some cretins and controls were kept in the same cage, so as to maintain the same conditions of food and environment; other cretins were kept in a cage alone so as to be spared the competition of the larger, more active controls. A few animals died spontaneously at early periods after operation, perhaps of parathyroid tetany, with no discovered anatomic lesions except those in the pituitary; and, as their pituitaries differed in no way from those of rats intentionally sacrificed, their pituitaries are included in the present series. All of the long-time cretins were killed with chloroform when in good condition, at the time interval desired up to 10 months after operation. Thirteen male cretins were studied (of these 4 died spontaneously), 12 female cretins (of these 3 died spontaneously), 3 rats thyroidectomized when adult, and 28 normal controls.

Pituitaries were weighed and then fixed in Helly's fluid. Serial sections were made at first, but it was found that the changes occurred quite uniformly throughout the pituitary, so that sections made from four different levels of each pituitary were adequate. Frequently control and cretin pituitary were mounted on the same slide so that both were subjected to identical staining conditions. The slides were stained with 10% acid fuchsin, rinsed in water, then stained with Mallory's aniline blue orange G mixture and then rapidly dehydrated in 95% and absolute alcohol. Hematoxylin and eosin staining is of little value, as basophils are not stained properly and a hyalin material stored within the cells stains pink and is indistinguishable from cell cytoplasm and granules. Giemsa staining was not found suitable. Various staining methods advocated for pituitary using acid violet were not found to give satisfactory staining for basophils in our hands. Formalin fixation gave poor results.

RESULTS. *Histologic Changes in the Pituitary.* Thyroidectomy performed in young rats results in the following characteristic sequence of changes in the anterior lobe. At the end of 7 and 9 days (Rats 3 O 8, 2 O 1, 4 J 7) there was no definite change. At 11 days Rat 2 O 2 showed increase in the number of large blue granular cells with accentuated outlines indistinguishable from the normal cells designated basophils.

By the 14th and 18th day (Rats T 1, 2 J 2) these basophilic elements were greatly increased in size and number (Fig. 2). In a few cells there appeared a definite vacuolization, and some were so full of fine vacuoles as to appear foamy. Occasionally there appeared to be a coalescence of smaller vacuoles to form larger ones. Many cells showed masses of a pale blue, homogeneous, hyalin material, in which empty vacuoles often occurred. The acidophils were distinctly decreased in numbers and in those that remained the granules were fading away so that it became very difficult to distinguish them from chromphobes.

By the 29th day (Fig. 3) in Rats O 5, R 8, R 4, most of the acidophils had disappeared. The majority of cells were altered cells with granules which stained indefinitely or distinctly blue, and these cells contained a large amount of hyalin material which often coalesced to form single globules of large size which almost completely filled the cells, pressing the nucleus to one side, while there still remained an equal number of finely vacuolated cells which did not contain hyalin material but rather a finely granular precipitate or remains of granular cytoplasm in an otherwise empty space. All intermediate stages between these two conditions were seen. Much less than half of the cells seen in the slide were chromophobes. No difference in fat content could be detected histologically in pituitaries 21 and 26 days after thyroidectomy (Rats 2 U 4, 2 U 2, 3 N 5).

At 33 and 35 days two rats (3 M 7, 3 G) showed the majority of cells to be large basophils. Where hyalin material occurred it was seen to be in basic staining cells.

At 37 days, in a very much dwarfed rat (R 5), the pituitary presented an astonishing picture (Fig. 4). Most of the cells were enormously altered. The transition was still more complete toward cells containing dense blue hyalin material, while some still showed fine coalescing empty foamy vacuoles. Only on close examination could basophils without vacuoles or hyalin material and chromophobes be identified. Very few acidophils could be found.

By the 48th day (Rat 2 N 1) the fine foamy vacuoles had nearly disappeared, and the cells had more the character of "castration cells," containing large homogeneous blue hyalin material, displacing the nucleus and cytoplasmic granules to one side. The hyalin varied in staining reaction, some appearing pale, some dark blue.

At 56 days, Rat 4 J 4 showed much the same appearance.

At 71 days (Rats 3 M 2, 3 B 4) the majority of cells had somewhat the "castration cell" appearance. Sometimes masses of cell granules were caught in the hyalin material, but usually cell granules were displaced to one margin of the cell (Fig. 5). The hyalin material became more dense and stained more deeply as time elapsed after thyroidectomy. Very few acidophils could be identified in Rat 3 M 2.

At 88 days Rat 3 H 2, which had been stunted in growth but which had started to grow again, and at 109 days Rat 3 D 1 and at 110 days Rat 3 A 3, which had never been dwarfed, were found to have thyroidectomy cells but showed the presence of many acidophils. Presumably a fragment of remaining thyroid had regenerated. These observations support the view that will be considered later, that the stunting of growth in the cretin is due to loss of acidophils. Acidophils were only found in considerable numbers in cretins when there was resumption of growth.

At 100 days in one rat (3 K 6) qualitatively the same changes were found as at 71 days but there seemed to be fewer thyroidectomy cells and more chromophobes. Again very few acidophils could be found.

One rat (3 J 6) was a cretin female which had been mated with a cretin male and gave birth to a healthy litter of young. She was killed 29 days later, 121 days after thyroidectomy. The pituitary showed the same changes (Fig. 6), in which the thyroidectomy cells resembled somewhat the so-called "castration cells;" but there were many acidophils in this pituitary. Had the fetal thyroid restored to a certain extent the maternal pituitary?

At 292 days Rat 2 V 2 showed considerable condensation of hyalin material and very few acidophils. There were more chromophobes than "thyroidectomy cells" at this stage.

No histologic differences in reaction of the pituitary could be detected between male and female rats.

Two rats (3 A 4, 3 A 5) that had been thyroidectomized when young but had never been stunted in growth were killed 110 and 124 days after operation. Their pituitaries showed abundant acidophils. No conspicuous vacuolation or hyalin material was present. Although no thyroid was found grossly at autopsy, presumably a slight amount was present which permitted body growth and prevented extensive changes in the pituitary. Apparently thyroidectomy (including aberrant thyroid tissue) must be complete, before extensive changes occur in the pituitary.

Only a few adult rats were thyroidectomized. In the young rats, the stunting of growth is proof of adequate thyroidectomy. In the adult rats this proof of adequate operation is out of question. Since we are at present interested in cretinism rather than adult myxedema we have not attempted the tedious and difficult procedures of basal metabolic rate determinations or serial sections of neck organs in

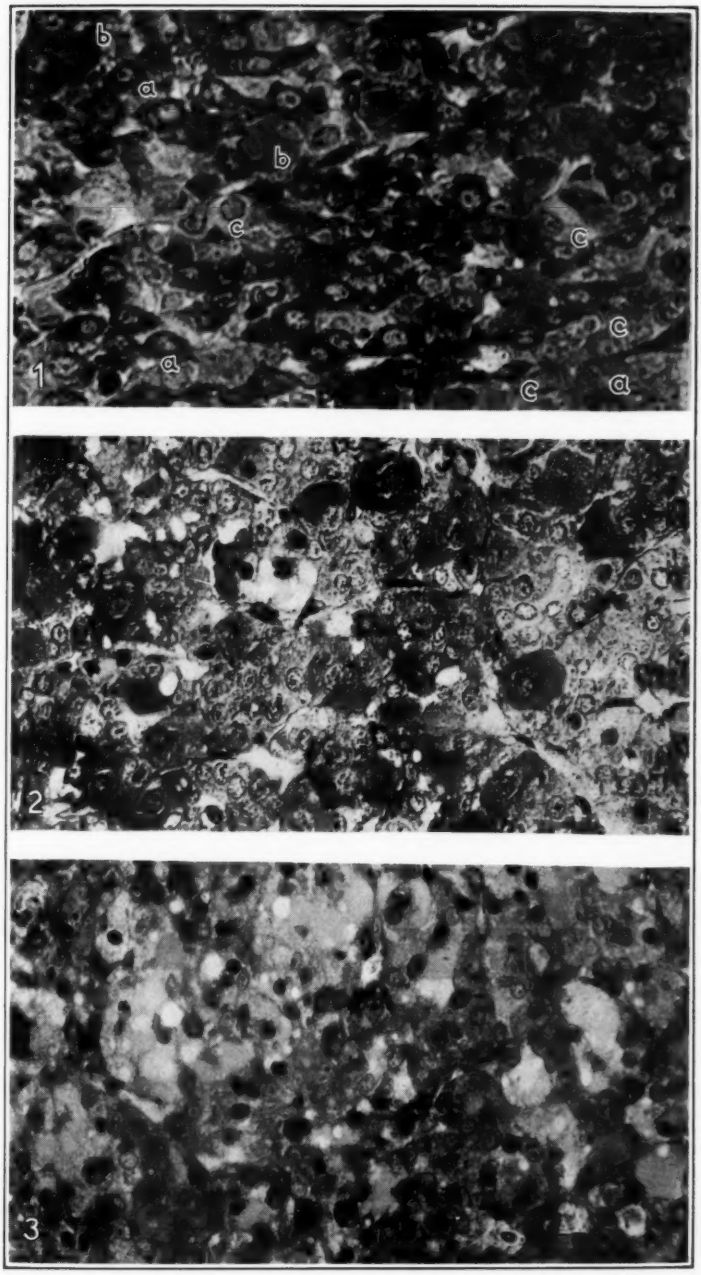

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FIG. 1.—Normal rat pituitary—R 9, as a standard of comparison for the subsequent illustrations. In a black and white photograph it is difficult to appreciate the distinction in cell types which are obvious in the stained section. The small dark cells (*a*) are acidophils, the large dark cells (*b*) are basophils, and the indefinite cells (*c*) are chromophobes. (Approximately × 566.)

FIG. 2.—Rat T 1 killed 14 days after thyroidectomy, showing prominent basophils which are increased in number and size. (× 482.)

FIG. 3.—Rat R 4 dying spontaneously 29 days after thyroidectomy. Vacuolization is advanced, and extensive deposition of hyalin material is seen. (× 482.)

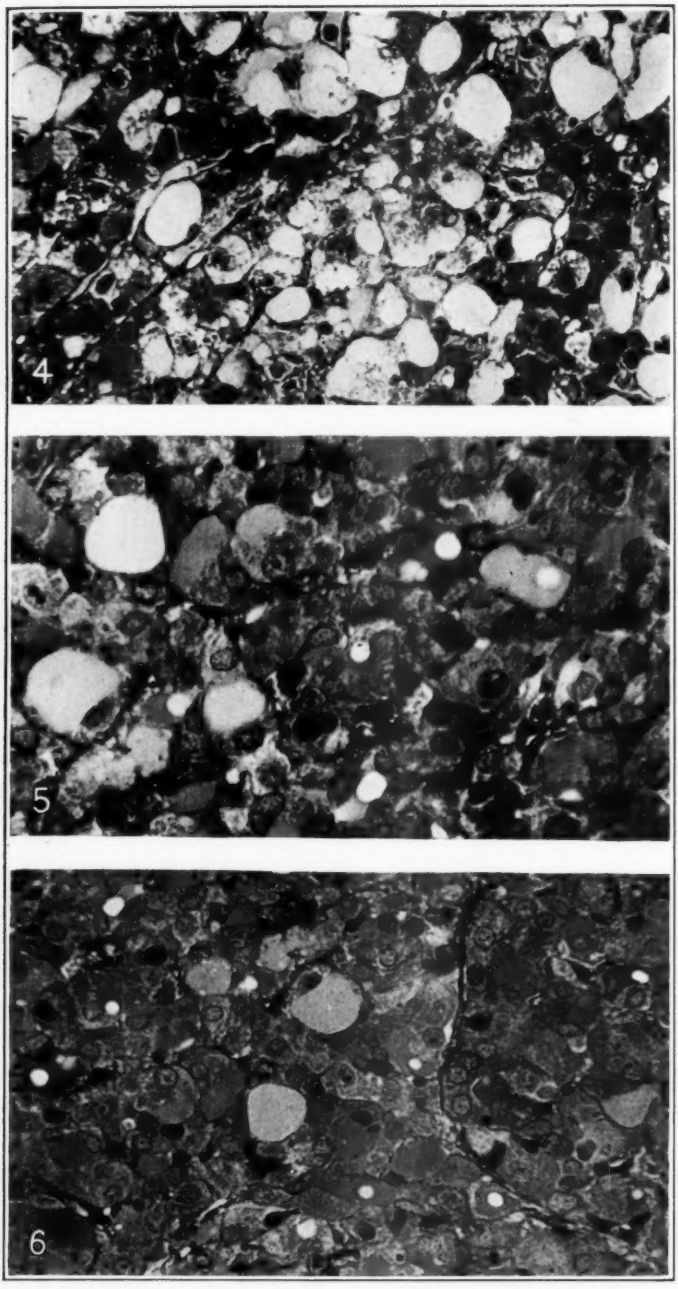

FIG. 4.—Rat R 5, markedly dwarfed and sluggish, was killed 37 days after thyroidectomy. The majority of cells contains a large amount of hyalin material which sometimes stains pale blue, sometimes darker blue. Many small, empty vacuoles are seen in cells, sometimes in the midst of hyalin material. Cell granules are seen in many cells in between vacuoles and sometimes in the midst of hyalin material. Acidophils have largely disappeared. (Ca. × 482.)

FIG. 5.—Rat 3 B 4, thyroidectomized at 161 days of age, and killed 71 days later. Hyalin material occurs in single dense globules within cells showing basic granules. Hyalin material varies greatly in intensity of staining. (× 566.)

FIG. 6.—Rat 3 J 6, killed 121 days after thyroidectomy. This rat had given birth to a litter of young 29 days before. "Thyroidectomy cells" bear some similarity to "castration cells." More acidophils were present in this pituitary than is usual in cretin pituitaries. (× 523.)

order to prove adequate thyroidectomy in the adult animals. However, granting these qualifications, it may be stated that 3 adult thyroidectomized rats have shown marked vacuolization of basophilic cells and hyalin deposit and reduction in number of acidophils (Fig. 5).

Pituitary Weights. It is repeatedly stated in the literature that the pituitary is increased in weight in cretin animals. We were interested in determining whether this increase was due to cellular or fluid increase. We also wished to see whether the cretin's pituitary was increased in weight above that of rats which were of the same body weight as the cretin but of a younger age.

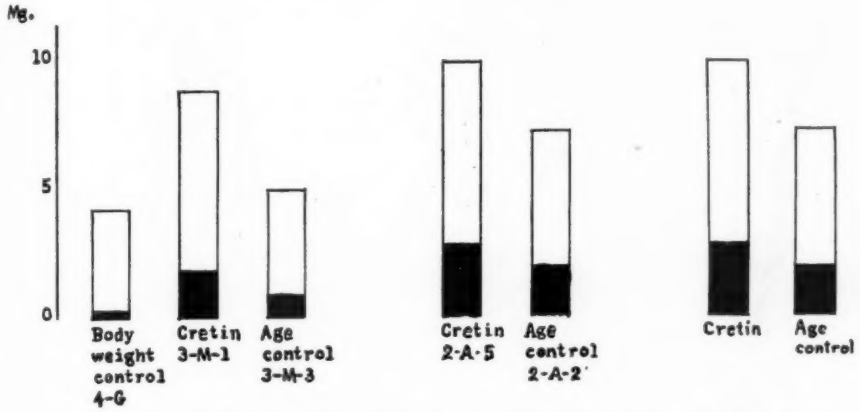

CHART I.—Fluid and solids in pituitaries of cretins and controls. The dark blocks indicate dry weights of the pituitaries, the height of the entire column the weight of the fresh pituitary before it was dried. The white block or difference between wet and dry weights represents fluid in fresh pituitary.

The pituitaries of several rats were weighed as soon as removed, dried in an oven at about 60° C. until the weights were constant, and left in a desiccator and weighed again. The difference between original and final weights represented fluid in the original gland. Chart I shows the results in 3 cretins with age controls and one body weight control. It will be seen that the cretin pituitary has a real increase in solid as well as in fluid.

Often the actual weight of the cretin pituitary is greater than that of the control rat, but sometimes there is only an increase in the percentage weight of the cretin pituitary (% of body weight).

When the weight of the pituitary is calculated in ratio to body weight of the rat and this value compared in the cretin with its age control, the degree of hypertrophy in the cretin reaches its maximum quite soon (Chart II).

When the actual weight of the pituitary, rather than its relation to body weight, is charted, and the cretin compared with rats of

similar body weight but younger rather than with rats of the same age (Charts III and IV), it is found that in the male the pituitary tends to be heavier than that of the normal rat of the same body weight, but that in the female there is some variation to this rule, probably because the pituitary in the female goes through cyclic changes in estrus.

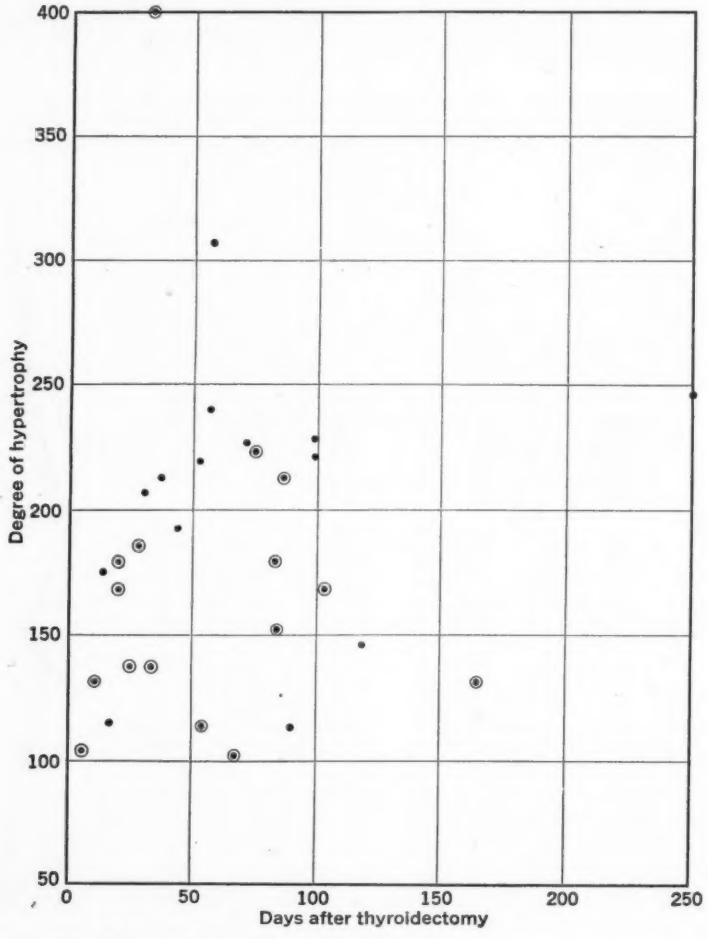

CHART II.—Degree of hypertrophy is expressed as $\frac{\%\text{ weight of pituitary of cretin}}{\%\text{ weight of pituitary of age control}} \times 100$ ⊙ Females. • Males.

Discussion. It is accepted that there are more pituitary hormones than there are histologic cell types in the pituitary. Presumably, therefore, cells of a given histologic type, such as the basophils, may elaborate more than one hormone, just as the simple acinar cells

of the pancreas elaborate several different enzymes. After thyroidectomy there is no question of the great increase in basophils, which to all appearances, when studied at varying time intervals, are the cells which develop the striking vacuoles and hyalin deposits. As time increases and the hyalin material becomes condensed in

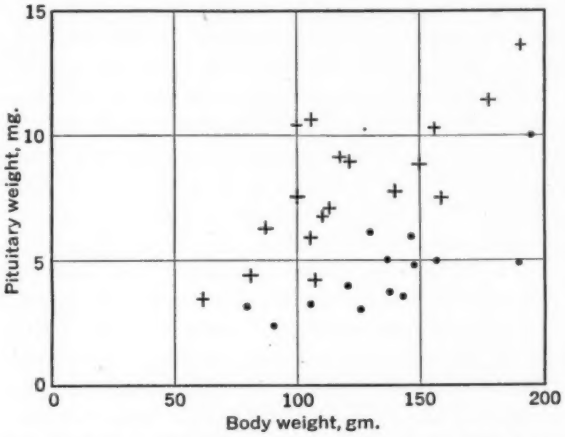

CHART III.—Pituitary weights plotted against body weights in male rats. + Indicates cretins; • indicates normal rats.

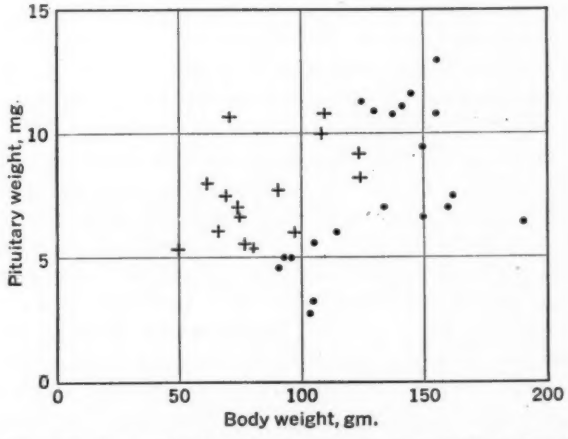

CHART IV.—Pituitary weights plotted against body weights in female rats. + Indicates cretins; • indicates normal rats.

single globules these cells come more and more to resemble the histologic appearance of "castration cells."

The first point for consideration in the interpretation of the "thyroidectomy cells" is whether they represent degenerative changes or secretory phenomena. Staining for fat revealed no

fatty degeneration. Moreover, the histologic appearance strongly suggests secretion if we compare them with the "castration cells" which have repeatedly been accepted as representing secretion. In work in progress it appears that pituitaries of cretin rats contain an abundance of thyrotropic hormone and this may represent an excess of thyrotropic hormone, if it is considered as the amount of hormone available per unit body weight of rat. The quantitative data will be given in a subsequent paper. From this result we feel justified in regarding much of the hyalin material as possibly accumulations of thyrotropic secretion, just as the hyalin material seen in castration cells of the pituitary has been shown by implantation experiments to represent an excess of gonadotropic hormones. This secretion of thyrotropic hormone in a hypothyroid animal seems reasonable in view of what is known of the physiologic principles of reciprocal relations between organs by which there is maintained a condition of equilibrium or "homeostasis" (Cannon[6]). When there is a lack of thyroid secretion therefore, it is possible that there should be a compensatory hypertrophy of those pituitary cells which form thyroid stimulating hormone, which would act upon any remnant of thyroid tissue that was present. Or the deposition of hyalin may indicate storage of thyrotropic hormone for which there is no utilization in the absence of the thyroid. In the normal rat pituitary isolated basophilic cells can be found containing hyalin material and this has been considered to be secretion of some sort. The "thyroidectomy cells" manifest this normal secretory appearance carried to great excess.

The histologic evidences of secretion and storage in cretin pituitaries seem greater than any changes in thyrotropic hormone content that was found on implantation of the pituitaries. The question therefore arises as to whether these cells are secreting and storing other hormones in excess. It soon became apparent that there were alterations in the weights of the adrenals and gonads in cretin rats, which suggested that there might be alterations in adrenalotropic hormone and gonadotropic hormone content of cretin pituitaries. Such studies are now in progress.

Morphologically there are distinct differences between the changes in the pituitary resulting from thyroidectomy and those resulting from castration. It is only at long intervals after thyroidectomy that the cells are somewhat similar to castration cells. The intracellular globules of "castration cells" are large, smooth, well defined, appear to be composed of dense secretion, hyalin in appearance when fixed and stained, and push to one side the basophilic granules in the cell, but in thyroidectomy cells the secretory accumulation has a less regular contour (Fig. 5). We have not seen in early stages of "castration cells" the characteristics observed in early stages of "thyroidectomy cells." In both cases, thyroidectomy and castration, there is preliminary to the formation of vacuoles a distinct

increase in large solid basophilic cells. In the castration pituitary, acidophils are abundant, in the thyroidectomized rat, acidophils are strikingly reduced.

The increased weight of the pituitary in proportion to body weight, and the fact that this increase is not due merely to increased fluid content, tends to indicate that this is not a degenerative change. It might be due to cellular hyperplasia or to increased content of a secretion which contains solids. It is apparent microscopically that there is at least a relative increase of cells of basic staining, and of chromophobes. Also, since the acidophils have largely disappeared and the pituitary is increased in weight, this increase in non-acidophil cells probably represents an absolute as well as relative increase of this cell type. The changed proportion in cell types suggests the probability of a corresponding change in proportion of hormones produced.

Another point for discussion is the disappearance of acidophil cells. This cannot be a matter of pressure atrophy, for in the castrate pituitary the basophilic hyperplasia is excessive and the entire gland is much enlarged, and yet the acidophil cells remain. After thyroidectomy, some regressive changes are seen in acidophils but these are not obvious. There seems to be a fading away of granules, in other words, a dedifferentiation of the cell, perhaps a reversion to the chromophobe type. The vacuolated and hyalin-containing cells show granules which are basophilic and there is no evidence that the acidophil passes directly to the vacuolated cell. Rather do the vacuoles seem to be a gradual change occurring in cells of indefinite or of basic staining. One point is definite: Since there is extensive disappearance of acidophils in the cretin pituitary, these cells cannot be the ones which produce the thyrotropic hormone, which is definitely present in large amounts in cretin pituitaries. This finding, we maintain, refutes the suggestion of Marine, Rosen, and Spark, who suggest that "the acidophilic granules contain the thyrotropic factor." Their statements, it should be noted, are based only upon histologic studies of the pituitary under various experimental conditions and not upon assay of pituitary potencies by implantation, such as we have carried out.

A point to be emphasized is that the stunting of growth of the cretin appears to be due to the extensive loss of acidophils. As far as we know, such an explanation for cretin dwarfism has not been stated in the literature. The reduction in numbers of acidophils has been reported in the literature, but attention does not seem to have been drawn to the relation of this to cretin dwarfism. It seems apparent from these experiments that the stunting of growth in the cretin has its immediate cause in the failure of the pituitary to produce growth hormone because of loss of acidophils which in turn is due in some way to the loss of thyroid secretion. Only in animals which are not stunted in growth did acidophils appear in

considerable numbers. The skeletal changes are different, to be sure, in cretinism and in pure hypophyseal dwarfism; but though qualitatively different, it is easily possible that the failure to obtain normal size is due to loss of acidophils in both instances. The association of acidophilic tumors or acidophilic hyperplasia with acromegaly has been taken as good evidence that the growth hormone is produced by acidophils. The reduction in acidophils in cretin dwarfism is another bit of evidence of a different type supporting the view that growth hormone is produced by acidophils.

Experiments are now in progress to determine whether the administration of thyroid extract will restore the structure of the cretin pituitary to normal.

It is a difficult matter to determine the origin of the "thyroidectomy cells." These cells must arise either as an alteration of one of the three standard types of cell or from a cell heretofore not recognized as an entity. We do not venture to postulate the latter. The vacuolation and hyalin deposition is preceded by distinct increase in numbers of basic staining cells which we cannot differentiate from the usual basophils. The dedifferentiation and then complete disappearance of acidophils concomitant with the rise in these thyroidectomy cells strongly suggest that the acidophils are the original source of the thyroidectomy cells; that perhaps they first become chromophobic in nature by loss of specific granules and then differentiate toward the basophil type. However, this is mere speculation, and an origin from newly formed basophils cannot be excluded. The absence of frank degenerative changes in the acidophils in the early stages when some are present suggests that they have become transformed in character rather than that they have been lost by atrophy and disintegration.

Previous Studies. Trautman[18] in a lengthy article reviews extensively the literature on pituitary changes after thyroidectomy up to 1916. From the more recent literature, as from the older, it is evident that there has been a lack of agreement as to which histologic type of cell is involved in the vacuolation, and whether this vacuolation is a retrogressive degenerative change or a hypersecretion. Only occasional studies, as that of Hohlweg and Junkmann,[7] and of Severinghaus, Smelser and Clark,[16] have been made in the light of our recent knowledge of the thyrotropic hormone. As examples of some of the differences of opinion may be cited the following:

The early German studies of the histology of the pituitary in human and experimental hypothyroidism were initiated by the idea that the pituitary and thyroid were similar histologically and functionally and that the pituitary probably showed compensatory hypersecretion in the absence of the thyroid. Rogowitsch,[12] in 1889, found that the pituitary of rabbits 1 to 10 weeks after thyroidectomy showed cells of increased volume with vacuoles, and colloid

material in the ground substance. He noted only slight changes in the chromophils. He interpreted the changes as both degenerative and hypersecretory. Stieda[17] in 7 thyroidectomized rabbits 1 to 12 weeks after operation saw no degeneration and no hyperplasia but a hypertrophy of the chief cells which showed vacuolization. He believed the changes were due to hyperactivity. He noted no changes in chromophils. Herring[5] found no changes in the anterior lobe of 3 thyroidectomized rabbits. Kojima[8] noted in thyroidectomized rats many large cells with vacuoles and hyalin substance. Ordinary "oxiphils" and "basiphils" were few. Poos[11] (extensive bibliography) found in thyroidectomized dogs and cats the appearance of a new cell as the chromophobes disappeared. These thyroidectomy cells he regarded as identical with "Schwangerschaftszellen" (pregnancy cells) and with castration cells. He stated that the eosinophils increased relatively and absolutely and he regarded this as an expression of hyperfunction. He found young animals reacted less than did old ones. Hohlweg and Junkmann[7] found after thyroidectomy of young rats the disappearance of acidophils and the appearance of vacuolated cells which looked like castration cells but which proved to be different when the gonadotropic potency of the pituitaries was tested. They also stated that cretin pituitaries showed no increased thyrotropic effect when injected into guinea pigs, but studied intervals after thyroidectomy up to only 20 days. Bryant[4] found in thyroidectomized rabbits a disappearance of acidophils and hypertrophy of chromophobes with later vacuolization and disintegration. He believed there must be decreased secretory function. Severinghaus, Smelser, and Clark[16] have recently described the changes in 9 thyroidectomized rats as "typical castration cells" with degeneration of acidophils and appearance of nuclear inclusions. Marine, Rosen, and Spark[10] have just published histologic studies on goitrous and on thyroidectomized rabbits. They found pituitary hypertrophy, and disappearance of acidophils, which they attribute to degranulation, but do not mention basophils or vacuolated "thyroidectomy cells." Although they used Mallory's stain for some slides, their photomicrographs are of sections stained with hematoxylin and eosin, and this staining method is such as to make it impossible to recognize the "thyroidectomy cells," because with eosin it is impossible to distinguish between the smooth hyalin intracellular material and the granular cytoplasm, and hematoxylin is inadequate for differentiating basophils.

Human autopsy material has been studied by a number of Germans. Wegelin[19] found that the pituitary of a cretin man aged 56 showed fatty degeneration of the chief cells, eosinophils and to a lesser degree of the basophils. Eosinophils and basophils were reduced in numbers. He describes the presence of many cells which he calls transition cells according to the terminology of Kraus,

larger than chief cells, with no granules and staining red with eosin. Abrikossof[1] found the pituitary of a woman aged 52 who had been myxedematous since 25 years of age to show an increased size of chromophil cells. MacCallum and Fabyan[9] found in the case of a 13-year-old cretin that the chromophobe cells were enlarged, the basophils very abundant and striking, and that some eosinophils were present but shrunken. Schilder[13] described in human hypothyroidism the appearance of a new cell which may develop from a chromophil or chromophobe. He regarded this cell as similar to Erdheim and Stumme's "Schwangerschaftszellen." He believed that there was probably increased activity and made the suggestion, keen considering the state of knowledge concerning the pituitary at that time, that the clinical manifestations of hypothyroidism are not to be attributed solely to the lack of thyroid but are attributable also to changes in the pituitary. Schultze[14] described in a case of aplasia of the thyroid in a woman aged 26 a reduction in number of acidophils and basophils with the presence of an adenoma of chief cells.

Summary. When thyroidectomy is performed in young rats there results stunting of body growth, an increased weight of the pituitary due both to increased solids and increased fluid content; a marked reduction or nearly complete disappearance of acidophils; an increase in the number of basic staining cells; and the appearance of great numbers of large cells filled with hyalin substance. These "thyroidectomy cells" appear, according to the special staining technique used, to be transformed cells containing blue granules.

The "thyroidectomy cells" appear to be secreting and storing a secretory product which is hyalin in appearance.

It is suggested that the stunting of body growth in the cretin rat may be due to loss of acidophils of the pituitary which in turn depends upon loss of the thyroid secretion. Acidophils seem to disappear by degranulation rather than by frank degeneration. An abundance of thyrotropic hormone was found to be present in cretin pituitaries depleted of acidophils, a finding which rules out the acidophil cell as the producer of thyrotropic hormone. Since there is no atrophy of the adrenals in cretin rats, it is reasonable to consider that the acidophils cannot be the producers of the adrenotropic hormone. When thyroidectomy is incomplete, the above changes are slight or absent.

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COMPLETE INSULIN RESISTANCE IN DIABETES.

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The announcement of the successful treatment of diabetes mellitus with insulin was hardly confirmed and put on a sound basis before there began to appear in medical literature reports of resistance to its action. Many of the earlier cases of so-called insulin resistance, however, could in the words of Labbé[1] be attributed to poor management or errors in interpretation.

On the basis of the experimental work of Hedon and McLeod on depancreatized dogs, Root[2] estimated that a completely depancreatized man would require 200 to 300 units of insulin daily. Undisputed cases of complete insulin resistance in man would then be those which have a daily requirement above this figure; *i. e.*, representing a complete replacement of the amount of insulin which

the body itself is capable of forming. A rather careful search through the literature reveals very few such cases excepting those which first come under observation when in coma and are given an enormous dosage before they either recover or die.

In 1927 Lawrence[3] reported the case of a 19-year-old boy, who had had diabetes for 2 years, whose insulin requirement had gradually risen, until, on a diet of carbohydrate, 115; protein, 80; fat, 150; he was excreting 55 gm. glucose in the urine despite 220 units of insulin daily. One day 400 units were given without inhibiting the rise of blood sugar after food. Insulin was then stopped for 5 days. At the end of this period the patient was in profound ketosis. He was rescued with insulin. For a time after this it was found that 80 units a day controlled the diabetes, although the requirement later rose to 160 units.

Glassberg, Somogyi and Taussig[4] described a case of a woman with diabetes which, beginning mildly, rapidly became more severe. At one time there was a skin sensitivity to insulin. The insulin requirement gradually increased over a 9-month period. In the course of the next 3 months she received an average daily dose of 317 units of insulin. In spite of this, acidosis occasionally intervened, requiring amazingly large dosage—1100 units in 1 day. Contrary to the usual experience 1 dose seemed more effective than divided dosage. This woman spontaneously improved and later behaved like an ordinary severe diabetic.

More cases of insulin resistance are reported in connection with hemachromatosis than with any other disease. Root[2] reported the case of a physician who had known hemachromatosis for 4 years. In the course of a few months he became increasingly resistant to insulin. In the last 1½ months of life the dosage was advanced progressively from 525 to 1600 units daily, without material benefit.

Allan and Constam[5] observed for 2 months a man with hemachromatosis who used 500 units of insulin daily. One of Wegener's patients[6] required 300 units of insulin daily to eliminate glycosuria. The case observed by Wood and Fitzhugh[7] continued to have glycosuria on 175 units daily and larger doses had little effect. Engel's patient[8] had had diabetes for 9 years, doing fairly well without insulin until a short time before admission in a precomatose state. The acidosis cleared with fairly small doses of insulin but the blood sugar remained high. Although the insulin dosage was advanced to around 200 units daily, the glycosuria persisted; shortly before death 1365 units were given in 1 day but sugar was found in the urine.

Karr, Skull and Petty[9] treated a diabetic who had a marked skin sensitivity to insulin. Her insulin requirement gradually increased, until, over a 4-month period she was receiving 470 to 620 units daily. Various kinds of insulin were given with no success. All tests indicated she was sensitive to insulin *per se*. Rabbits were

sensitized to the patient's serum. The patient was then given intramuscularly 5 cc. of this sensitized rabbit serum. In 1 week the insulin dosage was dropped to 150 units daily and after a month it was found possible to discontinue it.

That insulin may be comparatively ineffectual during acidosis is a very well-known phenomenon. A few cases which received an extraordinarily large dosage may be mentioned: Byworth[10] gave a diabetic with tuberculosis 1715 units. The patient was later discharged in good condition on 110 units daily. Labbé and Boulin[11] followed a case which received 3850 units in 13 days. Pollack and Long[12] report a case admitted in acidosis, successfully treated and carried for 6 days on 90 to 130 units daily. On the 7th day he relapsed into acidosis. He received 470 units this day and 540 units on the next. Because of a large thyroid gland iodin was given. The patient went into shock and died the following day. Necropsy showed thrombosis of all branches of the celiac artery.

Rudy[13] had a patient with mild diabetes who developed urticaria followed by temporary resistance to insulin. She was given 515 units in 24 hours. After this it was possible to decrease the dosage until none was required by the 11th day.

Falta and Boller[14] and MacBryde[15] working in Falta's Clinic, report a series of cases in which relative resistance to insulin is brought out. Mauriac,[16] Serio,[17] Häusler and Högler,[18] Umber and Rosenberg[19] and others believe in this type of partially resistant diabetes. Such resistance can be gauged by the lack of blood-sugar response to small or to large doses of insulin.

Case Report. M. P. (184535), a 44-year-old, white, divorced telephone operator, entered the San Francisco Hospital for the third time on June 11, 1934.

For several years she had had an intermittent dry cough. For a year this cough had been productive of sputum which later became blood streaked In 6 months she had had two hemoptyses of 2 ounces each. She had also developed night sweats, afternoon fever, weakness and easy fatigue. Several weeks before admission she was examined by a doctor who told her she had cavities in the lungs. She had lost 50 pounds in a year.

Family History. Was negative for tuberculosis. Mother had pernicious anemia.

Past History. Included pneumonia in 1904 and 1909, influenza in 1918. Diabetes was discovered in 1930. She was in this hospital in 1930 with the diagnosis of pelvic inflammatory disease. A supravaginal hysterectomy and bilateral oöphorectomy were done. She had on this admission some dysuria and nocturia.

Physical Examination. An emaciated pale woman lying in bed and coughing frequently. In the mouth were a few loose teeth. No lymphadenopathy. The chest showed bilateral wasting. There was dullness over both upper lobes, with flatness and tubular breathing over the right upper lobe anteriorly. Moist râles were heard through the right lung, a few râles at the left sternal border. The heart was not enlarged; sounds were loud and regular. Blood pressure 125/80. There was a hernia of a midline lower abdominal scar.

Laboratory. Hemoglobin, 73%; red blood cells, 3,900,000; white blood cells, 10,200 with 52% neutrophils. Urine, acid; specific gravity, 1.018; glucose 3+; acetone plus; few pus cells in sediment. Sputum repeatedly positive for acid-fast bacilli. Wassermann reaction negative. Sedimentation 28 mm. in 1 hour (Cutter). Fasting blood sugar 282 mg/100 cc.

Roentgen Ray Report. "Extensive pulmonary tuberculosis with multiple cavitation."

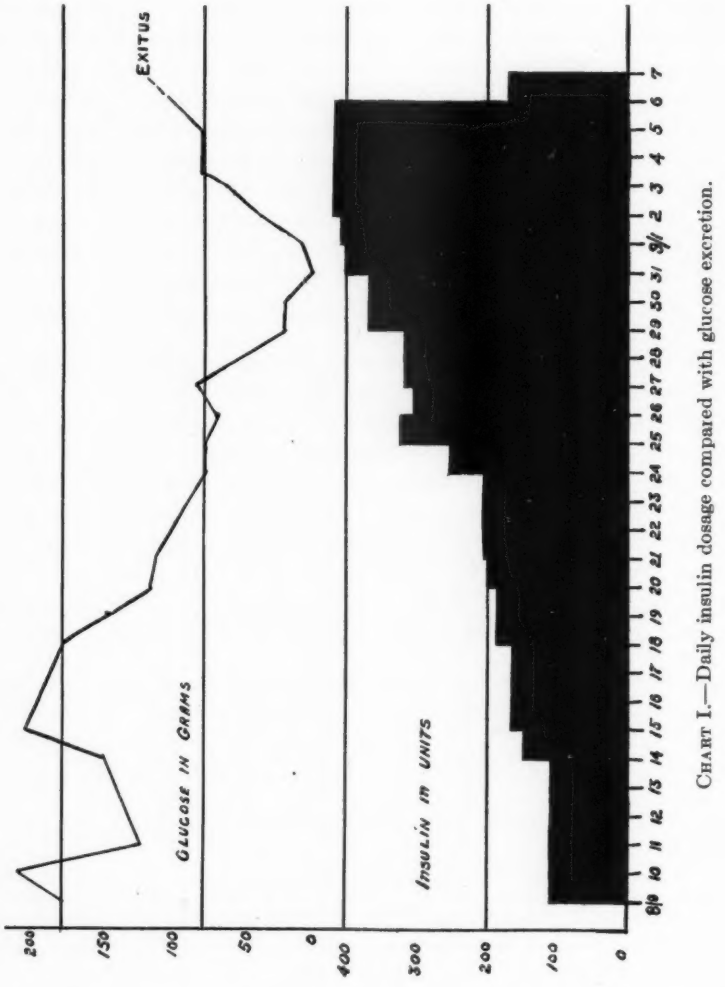

CHART I.—Daily insulin dosage compared with glucose excretion.

Course. She was never afebrile for more than a few hours, there was a daily rise to 99 or 100° F. with occasional elevations to 102°. The diabetes was at first controlled on a diet of carbohydrate, 175; protein; 75; fat, 75 with insulin 45–0–35–12 (92 units daily). A month after admission, while on the same intake, she began again to excrete large amounts of sugar into the urine. The fasting blood sugar which had been 143 mg/100 cc. rose to 256 mg. She was kept on the same diet and her insulin dosage

was increased. On August 15 she received 165 units of insulin and excreted 205 gm. glucose. By August 27 she was receiving 320 units daily while she excreted over 87 gm. glucose (Chart I). The diet was changed to 160–60–60 while the insulin dosage continued to be pushed up. For a time she seemed to be under better control, excreting only 7 gm. on August 31 while receiving 400 units of insulin. However, although she was being given 415 units daily, she again began to excrete more and more glucose, *e. g.*, 122 gm. on September 5. On September 6 she was reduced to 70 units. This day she excreted 125 gm. of glucose, had an urinary output (4345 cc.) considerably higher than it had been and a 4+ test for acetone in the urine. At 5.00 A.M. the next morning early signs of coma were observed. In spite of prompt efforts to relieve her (including another 100 units of insulin) she became unconscious at 8.00 A.M. and died at 11.45 A.M.

AUTOPSY (Dr. Alvin Cox). There are many adhesions over both apices, over the left diaphragm, through the posterior portion of the right pleural cavity and in the interlobar fissures. Extensive cavitation is found in both upper lobes. Caseous tuberculosis is found through both lungs, the left lower lobe being least affected. The peribronchial lymph nodes are moderately enlarged; some show a few gray nodules. The pancreas is grossly normal in size and appearance. The uterus has been amputated just above the cervix. The tubes and ovaries are surgically absent. The other organs are normal.

Microscopic Examination. Smears from the left pleural cavity show clusters of slender acid-fast bacilli. Sections from the lungs show variously areas of caseous pneumonia, fat-containing phagocytes, edema, conglomerate tubercles and fibrosis. There is slight fatty infiltration of the pancreas. The Islands of Langerhans and the acini appear normal. Special fixation and staining reveal no glycogen. The liver shows slight fatty infiltration but no glycogen. The kidneys show slight cloudy swelling and fatty infiltration. No glycogen is found. A peribronchial lymph node demonstrated several tubercles with giant-cell formation and caseation. The colonic mucosa contains eosinophils.

Comment. This woman was, before June, 1934, a diabetic of moderate severity who was also suffering from bilateral pulmonary tuberculosis, both of which were steadily advancing. On July 20 she was sugar-free on a diet of carbohydrate, 175; protein, 75; fat, 75; and 87 units of insulin. In the course of a very few days she showed very large amounts of sugar in the urine despite huge and increasing doses of insulin.

The attempt was made to keep her on a diet sufficient for the tuberculosis and to cover the deficiency of carbohydrate metabolism with enough insulin. For a time it seemed as though this might be successful. Later when it obviously was not, an attempt was made to reduce the insulin dosage abruptly.[3] This was, as is seen, followed by a quick exitus.

It is reasonable to suppose that had the insulin dosage been further increased, the result would have eventually been the same, as was the case with Root's patient.[2]

From a study of the chart it will be seen that this patient's ability to utilize sugar was enhanced by the use of extraordinarily large amounts of insulin, but that it was apparently impossible to keep her from excreting sugar into the urine until something happened

within her own organism to reduce her resistance. During this spontaneous partial remission very little glucose appeared in the urine. Then, on doses of insulin larger than before, her resistance again increased until there was as much sugar in the urine on 415 units daily as there had been 3 weeks before on 200.

However, the proof that the insulin, far in excess of what could be utilized, was serving a purpose is shown in the fact that within 18 hours after a smaller dosage was attempted the patient was in coma and within 28 hours she was dead—although the amount of insulin was still far in excess of that ordinarily sufficient.

Certain characteristics of the few cases of complete insulin resistance reported may be observed: (1) The resistance, as measured by the amount of insulin necessary to prevent glycosuria appears relatively quickly, usually over the period of a few months, and increases progressively. (2) The tolerance to insulin is usually proportional to the resistance—evidence of hypoglycemia is rare (in this case there were periods of asserted shock, unfortunately never checked chemically). (3) The obvious precipitating factors are various—severe liver and pancreatic disease, allergy, endocrine disturbance, and in this case, infection. It is interesting, that despite the relatively common occurrence of severe tuberculosis coincident with diabetes, no case of complete resistance in connection with infection was found in the literature. (4) There seems to be a tendency in some cases, at least, for the resistance to disappear spontaneously. It may almost be ventured that the phenomenon of complete resistance to insulin is an independent one, coincident with, rather than caused by the apparent etiologic factors, and disappearing after a period of time, if death has not been caused by the concurrent disease and provided enough insulin has been given during the resistance period. The remissions in the case of Glassberg and his colleagues have no apparent relationship to the treatment. Lawrence's case improved paradoxically after the cessation of insulin with the appearance of ketosis. A tendency to excrete less and later more glucose in the urine regardless of the insulin dosage may be seen in Chart I. Such reasoning may not hold good in hemachromatosis where anatomical changes are obvious and resistance seems concomitant with the end stages of the disease.

Although the etiology of resistance to insulin is not known, most observers agree in placing the responsible factors outside of the pancreas. Häusler and Högler[18] and Häusler and Loewi,[20] investigating the occurrence of an insulin-antagonistic substance in the blood, found that less glucose was taken up by human erythrocytes *in vitro* from the plasma of human insulin-resistant diabetics and from the plasma of dogs with the pancreas completely removed. They concluded that the cause of the resistance lies in the inaccessibility of the body cells to the action of insulin. This substance was

named "Glykämin."[21] Allan and Constam[5] failed to confirm these experiments.

Himsworth[22] has brought forth evidence to indicate that the insulin excreted by the pancreas is inactive and requires an unknown activator to transform it into utilizable substance. The absence of this companion substance in the blood could conceivably result in the phenomenon of insulin resistance.

That the liver plays a large rôle in the production of insulin resistance is indicated in the preponderance of cases with liver disease and by the importance of the liver in carbohydrate metabolism. The existence of an anti-insulin in the liver has been postulated[21] but has not yet been proven.

Summary. A case of diabetes mellitus, complicated by pulmonary tuberculosis, in which extraordinarily large amounts of insulin were insufficient to check the glycosuria, is presented. Death occurred after an attempt was made to reduce the insulin dosage. The case is regarded as an example of complete insulin resistance and is discussed in relation to other cases of insulin resistance previously reported.

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A STUDY OF BLOOD SUGAR OF EPILEPTICS.

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In 1924, Harris[1] called attention to the occurrence of hyperinsulinism and the resulting hypoglycemia. Subsequent papers by the same author[2,3] show that hypoglycemia is associated with convulsions similar to epileptiform seizures which in some cases have been diagnosed as epilepsy. As the data available on the blood sugar of epileptics are limited, it was felt that a study of a fairly large number of epileptics would be of value.

At Pacific Colony, a state institution for feeble-minded and epileptics, there are over 150 patients whose condition has been diagnosed as idiopathic epilepsy. From this group, 92 patients were chosen for fasting blood sugar determinations; 16 non-epileptic patients in the same institution, whose diet and living conditions were similar, served as a control group.

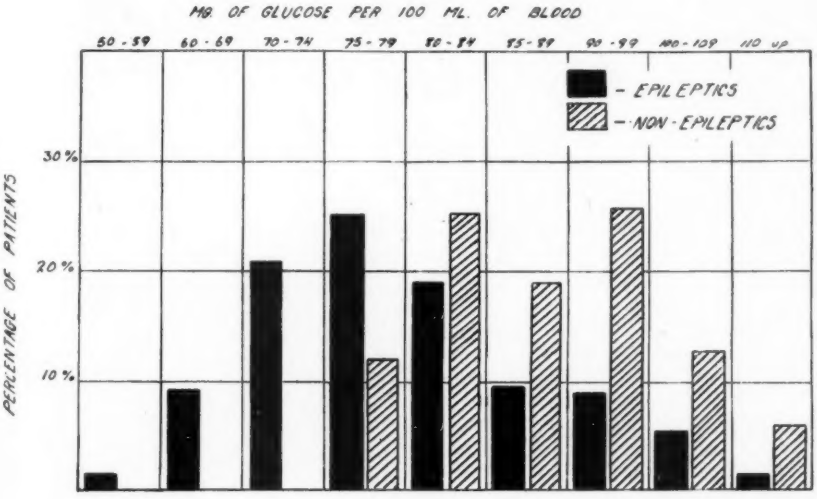
The blood samples were taken between 10.30 and 11.00 A.M., approximately 4 hours after breakfast. (This time was suggested by Dr. Harris in a private communication.) Five milliliters of blood were withdrawn from a vein in the arm and analysis was started immediately. The standard Folin and Wu method for the determination of glucose in blood was used throughout the study.

A summary of these tests is given in Chart I. It is apparent that as a group the epileptic patients showed an abnormally low amount of sugar in their blood. If 80 mg. of glucose per 100 ml. of blood is regarded as the lowest level for a normal fasting blood sugar value, 56.4% of the epileptic patients as compared with 12.5% of the control group show subnormal fasting blood sugar values.

In order to test the constancy of the fasting blood sugar level of epileptic patients, repeated determinations were made on 9 of the patients (Chart II). While a wide variation is seen, it is also noted that none of the patients showed a fasting blood sugar value that

was consistently normal; 11% showed values that were always subnormal; and 67% of the patients showed values that were normal only 50%, or less, of the times tested. While these results show that a single fasting blood sugar determination of an individual is of questionable value, the data obtained from such a large group seem to demonstrate the tendency of the group as a whole toward subnormal fasting blood sugar values, as do repeated fasting blood sugar determinations of an individual.

CHART I.—DISTRIBUTION OF FASTING BLOOD SUGARS FOR EPILEPTICS AND NON-EPILEPTICS.



Of the 92 epileptic patients whose fasting blood sugars were determined, 85 were receiving luminal (phenobarbital), as were the 9 patients whose fasting blood sugars were rechecked over a period of time. The dosage varied from 0.5 to 4.5 grains daily. It has been suggested that perhaps the drug itself functions in raising the blood sugar level.[3] To investigate this possibility, a non-institutionalized control took two 1.5 grains of luminal during a period of 12 hours. This resulted in an increase of 7% in the fasting blood sugar level, which was normally very constant and on three different tests covering several months showed a variation of less than 1%. When the symptoms caused by the drug began to wear off, the blood sugar value dropped slowly. While this is not conclusive evidence that luminal does raise the blood sugar level, it at least supports an existing theory. If luminal actually does raise the blood sugar level, there would be more than 56.4% of the epileptic patients showing subnormal sugar values if luminal therapy were not used.

Glucose tolerance tests were made on 7 epileptic patients who were chosen because of their normal mentality and willingness to

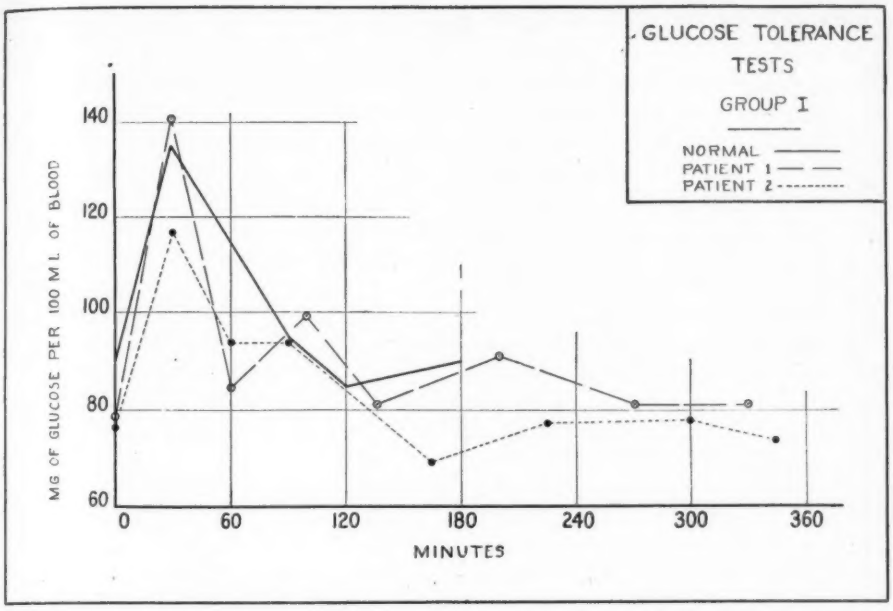
coöperate in the experiment. Although they were ordinarily on luminal therapy, the drug was not given the night preceding nor on the morning of the test, nor was smoking allowed. The fasting blood sugar was taken at about 8.00 A.M. Immediately thereafter the patient drank a 50% solution containing 100 grams of glucose. Sugar determinations were made at approximately half-hour intervals for the first 2 hours, and at hourly intervals for the following 4 hours.

CHART II. VARIATION IN FASTING BLOOD SUGAR VALUES.

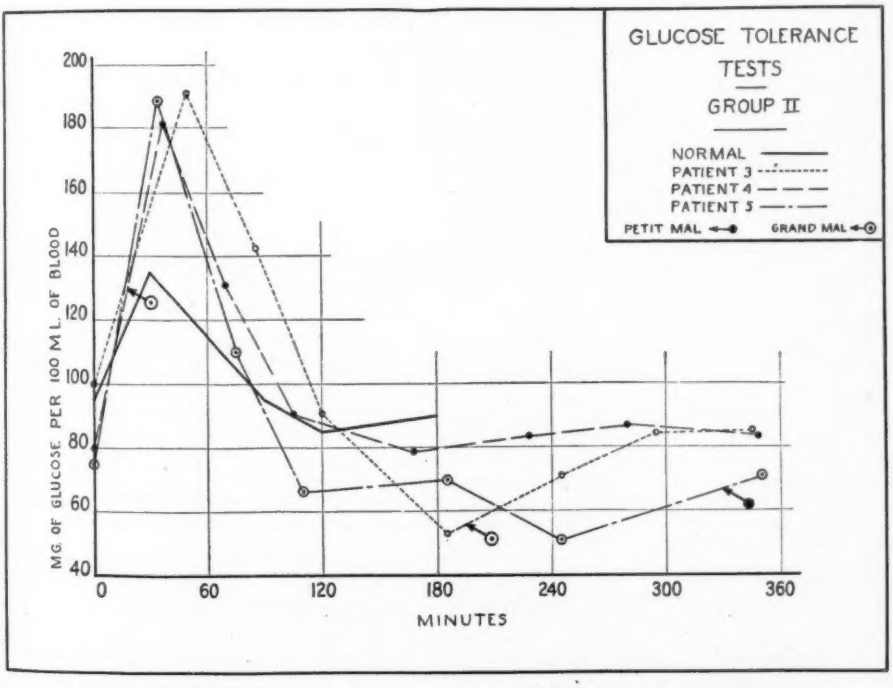
Patient number.	Date (all in 1934).	Blood sugar in mg. per 100 ml. of blood.	Per cent of difference between lowest and highest value.	Per cent of the times tested when normal sugar values were obtained.
1	4/9	111		
	5/7	69		
	5/10	90		
	6/22	80	39	75
2	4/9	98		
	5/7	95		
	7/5	76	29	67
3	4/9	90		
	5/7	76		
	5/10	76		
	7/6	100	31	50
4	4/9	104		
	5/7	73		
	5/10	79		
	7/27	80	42	50
5	5/10	73		
	5/13	66		
	7/20	75	13	0
6	5/31	74		
	10/12	90		
	10/26	76	22	33
7	4/9	94		
	5/7	72		
	6/29	82	30	50
8	4/9	69		
	5/7	74		
	7/13	76	10	0
9	4/9	86		
	5/7	62		
	5/10	88	45	67

The experimental curves obtained from the glucose tolerance tests fall into three groups, as shown by Graphs I, II and III. On the three graphs the experimental curves are contrasted with the normal curve taken from Bodansky.[4]

Group I. Curves that do not deviate greatly from the normal curve. Patients in this group average but one grand mal seizure every 2 months.

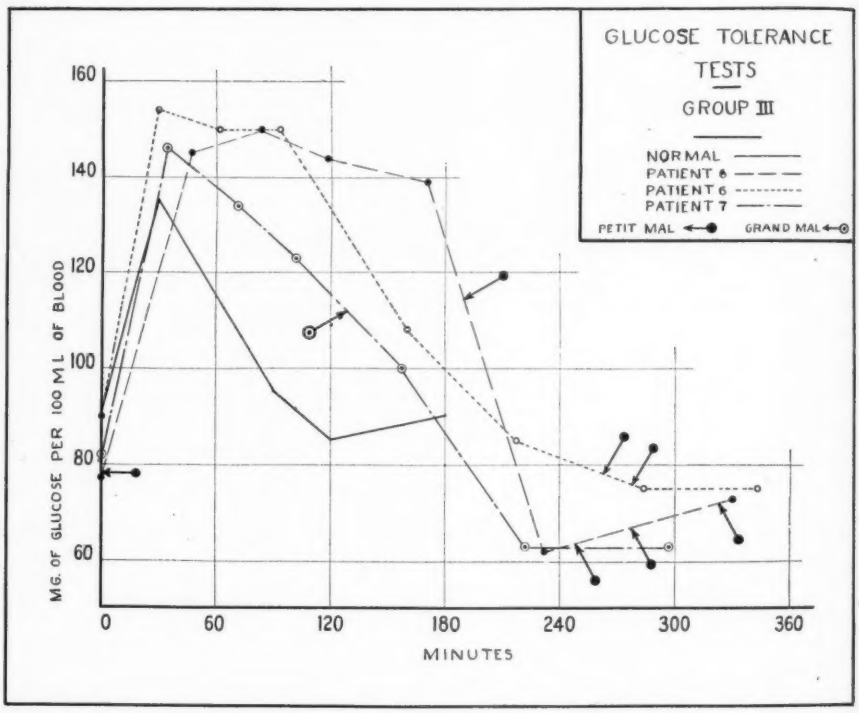


GROUP I. Type of curve nearest normal. No seizures occurred during test. In the first 11 months of 1934, Patients 1 and 2 each had 5 seizures.



GROUP II. Abnormal type of curve. Patient 3 had 2 grand mal seizures and Patient 5 had 1 petit mal seizure during the test. In the first 11 months of 1934, Patient 3 had 44, Patient 4 had 13, and Patient 5 had 35 grand mal seizures. Patient 5 also had many petit mal seizures.

Group II. Exaggeration of peaks and valleys. Curves whose maximum peaks are from 40 mg.% to 50 mg.% higher than the normal peak and whose minimum values are from 5 mg.% to 34 mg.% lower than the normal curve. The general contour of the experimental curves is similar to the normal one, but the peaks and valleys are greatly exaggerated. The patient (Case 4) whose minimum value is only 5 mg.% below the normal amount, averages but one grand mal seizure per month. The patients (Cases 3 and 5) whose minimum values are 31 mg.% and 34 mg.% below the normal value average from 3 to 4 grand mal seizures per month.



GROUP III. Most abnormal type of curve. Patient 6 had 3 petit mal seizures during 1 test, and 5 petit mal seizures during the second test several weeks later. Patient 7 had 1 grand mal seizure during the test. Patient 6 had 9 grand mal seizures from the date of his admission, May 19, to December 1, 1934, and in addition had averaged about 5 petit mal seizures per day. Patient 7 had 68 grand mal seizures in the first 11 months of 1934.

Group III. Delayed return to minimum values which are subnormal. Curves which rise similarly to the normal curve for the first half hour but which do not return to the minimum value for from $3\frac{3}{4}$ to $4\frac{3}{4}$ hours instead of the 2 hours exhibited by the normal curve, and the minimum values are much lower than shown in the normal curve. One patient in this group (Case 6) averages about

2 grand mal seizures per month and 5 petit mal seizures per day. The other patient in this group (Case 7) averages 6 grand mal seizures per month. It should be noted that two tests were run on Patient 6 and very similar curves were obtained in each case.

Summary. Abnormal carbohydrate metabolism appears to be associated with at least one type of epilepsy, as shown by the two series of tests here presented.

1. A study of the fasting blood sugar level of 92 epileptic patients showed that although 85 of them were on luminal therapy, which may cause a rise in the fasting blood sugar level, 56.4% of the group showed subnormal fasting blood sugar levels as compared with only 12.5% of the non-epileptic control group.

2. The glucose tolerance tests pointed strongly to the fact that there is a correlation between abnormal glucose tolerance and the frequency of the seizures experienced by the patients, both during the test and during the patients' institutional life. However, the seizures that occurred during the tolerance tests were as likely to occur at medium as at low blood sugar values. Three types of response to the sugar tolerance test by epileptics are discussed.

We wish to express our appreciation for the assistance given the writers by Mr. H. L. Roberts, Mrs. Pearl McRae and Mrs. Dorothy K. Tyson of Pacific Colony, and by Dr. L. W. Case of the Pomona Valley Community Hospital. Without their generous coöperation this study would have been impossible.

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THE RELATION OF EXPERIMENTAL SKIN INFECTION TO CARBOHYDRATE METABOLISM.

THE EFFECT OF HYPERTONIC GLUCOSE AND SODIUM CHLORID SOLUTIONS INJECTED INTRAPERITONEALLY.*

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THE occurrence of infections of the skin, often of unusual severity, is frequently noted as a complication of diabetes (van Noorden

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and Isaac,[1] Greenwood[2]). Aside from the vascular disease which is sometimes present, an adequate explanation of this phenomenon is lacking and there has been surprisingly little study of it experimentally. It has also been proposed, but not definitely established, that skin infections may occur as a result of excessive ingestion of carbohydrates by non-diabetic individuals.

The presence of increased amounts of glucose in the skin cannot apparently be regarded as the sole explanation of the lessened resistance of diabetics to infection. Greenwood and Rockwood,[3] on the basis of a study of a series of diabetic patients having an average blood sugar of 198 mg. over a period of 5 years, found that only 5% of such patients developed skin infections, although fungi were recovered from the feet of 70% of their cases and staphylococci from the feet of 100%. They conclude that some other factor than the hyperglycemia must be operative. Fabry[4] has expressed a similar opinion.

Richardson[5] has recently demonstrated that the blood of diabetics is deficient in antibacterial power, due to an impairment of the amboceptor rather than from any lack of activity of the complement. He found that this was true of both the natural amboceptor as shown by bactericidal tests and the acquired amboceptor as shown by the increased ability of the blood to form agglutinins. Kleinschmidt[6] found that diets excessive in carbohydrates or fat produced no marked difference in antibody formation in non-diabetic dogs. Handmann[7] has shown that blood to which 0.5 to 1.5% of glucose was added maintained its bactericidal power for staphylococci *in vitro*.

We have encountered only a single study of the effect of glucose on experimentally induced infection. Franceschelli[8] has observed a heightening of the virulence of streptococci when phlorizin diabetes was induced in rabbits. No effect on the virulence of staphylococci was noted, however, nor did the injection of large amounts of glucose into phlorizinized rabbits result in any change in the virulence of bacteria.

Cornbleet[9] has observed a retardation of the self-sterilizing powers of the skin following administration of 50 to 100 gm. of glucose daily to patients. Since the degree of retardation appeared to be related to the slowness with which the blood sugar returned to the fasting level, Cornbleet believes that the infections of the skin which he has observed in patients with a lowered carbohydrate tolerance may be dependent on this factor. Usher[10] has shown that increases of sugar in the sweat of diabetics may lead to more favorable conditions for the growth of fungi and bacteria.

Numerous attempts to demonstrate a connection between decreased carbohydrate tolerance and infections of the skin by means of fasting blood-sugar determinations and glucose-tolerance tests have been made. The results of such studies are contradictory,

as will be seen from the summaries of the literature by Fischer[18] and by Rudy.[21] Pick,[11] Müller,[12] Simon,[13] Devoto,[14] Benet and Nepveux[15] have reported increased blood-sugar levels in patients with furunculosis; Schamberg and Brown,[16] Rost,[17] Fischer,[18] and Narducci[19] note no significant increase; while Tauber[20] reports hypoglycemia to be a frequent finding and has noted a favorable response to intravenous injections of glucose in furunculosis.

To summarize this brief review of pertinent studies, most of which are as yet unconfirmed, it is indicated: (1) that while diabetics show a somewhat increased incidence of skin infections, some severe diabetics may have an entirely normal resistance to such infections and that the presence of increased glucose in the skin is not, apparently, the sole reason for decreased resistance to infection, (2) that the blood of diabetics is deficient in antibacterial power, but (3) that a heightened intake of carbohydrate in normal dogs leads to no marked decrease in antibody formation and that the simple addition of considerable quantities of glucose to blood does not lessen its bactericidal power for staphylococci; (4) that phlorizin diabetes heightens the virulence of streptococci but not of staphylococci in rabbits; (5) that administration of glucose in humans apparently decreases the self-sterilizing power of the skin; and (6) that it is doubtful whether or not decreased carbohydrate tolerance is more frequently encountered in patients with skin infections than in normal individuals.

In view of the contradictory nature of much of the clinical evidence concerning the influence of carbohydrate on skin infections and the marked paucity of experimental evidence, particularly in animals, we have undertaken a study of the effect of parenteral administration of comparatively large amounts of glucose on the course of experimentally induced skin infections in rabbits.

Method. Considerable preliminary work on the method of consistently producing skin infections was necessary. We obtain only an occasional infection following intradermal injection of a suspension of Trichophyton gypseum in rabbits. Using various strains of staphylococcus and streptococcus injected intradermally in broth suspension, infection was obtained in a large proportion of rabbits with staphylococcus, but in less than half the animals with streptococcus. A greater or less degree of reaction was present in all animals injected with a bacterial suspension, but based on the criterion of recovery of the organism, successful inoculation was considerably less using streptococci than with staphylococci. In successful infections the degree of reaction to staphylococcus was greater than that to streptococcus. There was no evidence of symbiotic effect when the two organisms were injected mixed in the same broth suspension. The degree of reaction, while somewhat dependent on the amount of bacterial suspension injected, was not nearly proportional to it. Intradermal injection of sterile broth medium produced no reaction.

By successive inoculation and recovery of the organism from rabbits we obtained a strain of S. aureus hemolyticus originally isolated from a case of pyodermia, which always produced definite infection in the skin when injected intradermally. In normal rabbits, following intradermal injection

of 0.5 cc. of a broth suspension of the organism, the resulting infection varied from an inflammatory nodule 3 cm. in diameter, with a small central ulcer, to an ulcer 3 cm. in diameter surrounded by an indurated inflammatory border 0.5 to 1 cm. wide. Infections of the latter extent were uncommon, only 3 such being encountered in control rabbits. Twenty-four-hour broth cultures were used throughout, no bacterial count being done on the suspensions. In each set of experiments the same suspension was used for intradermal injection in both the control and the glucose-injected animals. While none of the data here presented are based on observation of rabbits previously infected, we noted no evidence of acquired resistance to the organism following repeated infection of the same animal.

FIG. 1.—Infection of skin of normal rabbit 72 hours after intradermal injection of suspension of hemolytic Staphylococcus aureus.

Varying amounts of 50% glucose solution were injected intraperitoneally at varying intervals in animals infected intradermally. The initial injection of glucose was made within a few minutes after the injection of the suspension. The infection was produced high on the abdomen and the intraperitoneal injections given low down, well away from the site of infection.

Exact interpretation of the degree of inflammatory response following intradermal injection of a bacterial suspension is difficult because of the variation of the infection in control rabbits and because of the variety of criteria which may be considered. It was felt, after considerable observation, that the extent of the resulting ulceration represented the most reliable

and significant change. The extent of the inflammatory response did not always forecast a severe destructive change. The duration of the infection until definite involution was noted was a helpful criterion, but in our later experiments the rabbits frequently did not survive until healing had begun.

FIG. 2.—Extensive necrotic infection of the skin of rabbits receiving 24-hour total of 15 gm. glucose per kilo injected at intervals of 4 hours. Skin infected 36 hours previous to time of picture.

Results. In Table 1 it is seen that intraperitoneal administration of as much as 7.5 gm. of glucose per kilo in 2 doses in 24 hours did not affect the course of the experimentally produced staphylococcic skin infection. While such injections constituted a large total dose of glucose, it was found that the blood sugar was raised during only about 10 hours of the 24. It was therefore decided to produce a more continuous and marked hyperglycemia by frequent injections of glucose although the possibility of producing changes in water balance was apparent. It was found that following an injection of 2.5 gm. glucose per kilo the blood sugar returned to normal in about 5 hours. Repeated injections were therefore given every 4 hours. The peak of the blood sugar rise was reached in about 30 minutes after injection and in 4 hours the value was usually above 200 mg.%. While we were not able to follow fre-

quently the blood-sugar values over a period of 36 to 48 hours, our data indicate heightening of the peak of the blood sugar following successive injections, a slower fall toward normal, and an increasing failure to approximate the normal level.

TABLE 1.—THE EFFECT OF INJECTIONS OF GLUCOSE INTRAPERITONEALLY AT INTERVALS OF 24 AND 12 HOURS ON THE EXPERIMENTAL SKIN INFECTION.

Exp.	No. of rabbits.	Glucose per kilo, total in 24 hours.	Injection interval, in hours.	Duration of exp. in days.	Course of skin infection.
I	2 injected 1 control	2.5 gm.	24	4	All infection in normal range; infection in one glucose animal more, and in other less marked than in control.
II	2 injected 1 control	4.0 gm.	24	5	Infection of one glucose animal slightly more marked, the other less marked than control.
III	3 injected 3 controls	4.0 gm.	24	6	Two glucose animals showed less reaction than all controls; one showed more reaction. All infections within usual limits of control animals.
IV	3 injected 2 controls	7.5 gm.	12	6	All infections within usual limits; one control showed slightly more reaction than glucose animals, the other slightly less.
V	3 injected 2 controls	7.5 gm.	12	6	All within usual limits.
VI	2 injected 2 controls	7.5 gm.	12	6	All within usual limits.

TABLE 2.—THE EFFECT OF INJECTIONS OF 50% GLUCOSE INTRAPERITONEALLY AT 4-HOUR INTERVALS ON THE EXPERIMENTAL SKIN INFECTION.

Exp.	No. of rabbits.	Glucose per kilo, total in 24 hrs.	Injection interval, in hrs.	Course of skin infection.	Result.	No. of injections.
VII	4 injected	15 gm.	4	No. 1: ulcer 10.5 x 9 cm. 36 hours after first glucose injection	Recov.	11
				No. 2: ulcer 11 x 12 cm. 30 hours after first injection; marked diarrhea	Died	6
				No. 3: ulcer 14 x 12 cm. 30 hours; marked diarrhea	Died	7
				No. 3: ulcer 13 x 10.5 cm.	Recov.	11
	4 controls	...	...	All infections within usual limits		
VIII	4 injected	15 gm.	4	No. 1: ulcer 8 x 8 cm.	Died	9
				No. 2: ulcer 4 x 3 cm.	Died	11
				No. 3: ulcer 8 x 10 cm.	Recov.	10
				No. 4: ulcer 6 x 8 cm.	Died	10
	3 controls	...	...	All within usual limits; no ulcer over 1.5 cm. in diameter in 48 hours		

Eight rabbits were given 2.5 gm. glucose per kilo every 4 hours for periods varying from 36 to 48 hours. The skin infection of all 8

showed not only a marked variation in extent as compared to control animals but also a difference in character, consisting of a lessened degree of inflammatory reaction at the periphery of the infected area and a gangrenous necrotic appearance of the ulcer with less production of frank pus. The entire course of the infection was one of astoundingly rapid advance, with demonstrably less evidence of local tissue resistance to the infection.

FIG. 3.—Skin infection 36 hours after intradermal injection of staphylococcic suspension in rabbit receiving hypertonic NaCl solution intraperitoneally at intervals of 4 hours.

Of these 8 rabbits 5 died in from 3 to 7 days after the initial injection of glucose. Postmortem examination revealed little or no peritoneal fluid; a small amount of free pus was present in one animal in which perforation of the large bowel was present. The liver, spleen, pancreas, and intestines of the animals were grossly normal. Routine hematoxylin and eosin sections of the liver revealed no marked changes.

To determine whether or not the hypertonicity of the injected glucose was responsible for the marked increase in the extent of the infection in animals injected frequently, control experiments were performed in which a solution of sodium chlorid of approximately

the same tonicity as 50% glucose solution was injected. It will be seen from Table 2 that the extent of the skin infections following such injections was markedly greater than in normal rabbits and that it closely approximated the infection noted after frequent injections of glucose. In 4 animals, two of which received 4% NaCl and two 2% NaCl solution, the course of the skin infection was similar to that of the control animals.

TABLE 3.—THE EFFECT OF INJECTION OF NaCl SOLUTION OF VARYING STRENGTHS INTRAPERITONEALLY ON THE EXPERIMENTAL SKIN INFECTION.

No. of rabbits.	Strength NaCl, %.	NaCl in cc.	Injection interval in hrs.	Course of skin infection.	Result.	No. of injections.
4	9	10	4	No. 1: ulcer 5 x 7 cm.	Recov.	8
				No. 2: ulcer 9 x 7 cm.; markedly toxic	Died	6
				No. 3: ulcer 6 x 7 cm.	Died	8
				No. 4: ulcer 3 x 4 cm.	Recov.	8
2	4	10	4	No. 1: ulcer 2 x 2 cm.	...	12
				No. 2: ulcer 1.5 x 2 cm.	...	12
2	2	10	4	No. 1: ulcer 1 cm. in diameter		
				No. 2: ulcer 1.5 cm. in diameter		
2	—Control—			No. 1: ulcer 2 cm. in diameter		
				No. 2: ulcer 1.5 x 2 cm.		
3	9	10	4	No. 1: ulcer 5 x 3 cm.	Died	6
				No. 2: ulcer 4 x 4 cm.	Died	7
				No. 3: ulcer 8 x 10 cm.	Recov.	10
2	—Control—			Neither ulcer over 2 cm.		

Comment. It is apparent from these results that the injection of glucose in a dose of 7.5 gm. per kilo divided into 2 doses during 24 hours did not influence the course of the experimental skin infection in rabbits. Such injections were continued for 6 days and, if anything, the trend in glucose-injected animals was toward more rapid healing of the skin. With increase of the dose of glucose to a total of 15 gm. per kilo divided into 6 doses during 24 hours, a marked increase in the extent of the skin infection was noted within 24 hours and often within 12. After the infection was well established in these animals, its advance was often evident grossly during a 4-hour period. In rabbits receiving similar amounts of 9% sodium chlorid intraperitoneally, the skin infection closely approximated that seen when glucose was used, indicating that a specific effect of glucose as such was not the chief factor involved. It would seem entirely probable that the changes observed were due to a disturbance in fluid balance in the animal. Whether or not a change in the fluid balance of the skin itself led to the marked decrease in its resistance to infection is not evident.

It is obvious that experiments involving frequent injections of a hypertonic solution are drastic and unphysiologic. In the initial experiments in which less frequent injections were given, the animals

only occasionally became toxic, with more or less severe diarrhea. In these animals, in spite of a total glucose dosage of 7.5 gm. per kilo in 24 hours, which in a 60 kilo man would represent an intake of 450 gm., no change in the course of the experimental infection was observed. It would seem that extreme and drastic conditions must be produced before the experimental skin infection is influenced greatly. All the animals receiving hypertonic glucose or sodium chlorid solution at frequent intervals eventually showed some evidence of toxicity, varying from slight listlessness to marked exhaustion. Moderate to severe diarrhea was always present and the urinary output was considerably increased. No direct correlation between the objective evidence of toxicity and the extent of the skin infection was noted; quite as commonly very toxic rabbits showed less evidence of skin infection than animals in which the injections were relatively well borne. In this connection we had the opportunity of observing several animals which contracted pneumonia shortly after the skin was infected. Although almost all the animals died, the extent and course of the skin infection was entirely comparable to that seen in normal rabbits.

Summary. The parenteral administration of glucose at 12-hour intervals in a dose of 7.5 gm. per kilo for a period of 6 days had no effect on an experimental staphylococcic skin infection in the rabbit.

When the dose of glucose was increased to a total of 15 gm. per kilo in 24 hours, given at intervals of 4 hours, a very marked increase in the extent of the experimental skin infection was noted (within 24 hours).

A similar effect was noted following injection of sodium chlorid solution of the same tonicity and in similar amounts.

An investigation of the effects of dehydration and acidosis on experimental skin infection is planned, as well as that of glucose administered by mouth.

We wish to acknowledge the valuable technical assistance of the Pepper Laboratory of the University Hospital in the bacteriological phase of this study.

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LYMPHOPATHIA VENEREUM.
(Lymphogranuloma Inguinale).
And Its Relation to Rectal Stricture.

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The cases of lymphopathia venereum considered in this communication were seen at the Pennsylvania Hospital during the past 2 years. The studies of DeWolf and VanCleve[1] and Cole[2] of Cleveland have brought this subject to the attention of the medical profession of this country. Sulzberger and Wise[3] have suggested the name lymphopathia venereum. It is a less confusing and more accurate term than lymphogranuloma inguinale and we have adopted it.

Lymphopathia venereum is a chronic venereal disease, caused by a filterable virus.[4,5] The transient and often herpetiform primary lesion of the skin is followed, in from 2 to 6 weeks, by the development of a characteristic subacute or chronic inflammatory reaction in the regional lymph nodes. Suppuration usually occurs; fistulas and sinus formation are common. The disease is primarily lympho-

tropic in nature. Rarely a localized cutaneous form is seen.[6,7] Authentic extragenital cases have been recently reported.[8,9]

In the early stages a constitutional reaction, of varying severity, may occur. It is rarely seen in temperate climates, where the disease seems to run a comparatively milder course. In the tropics and in the European countries chills, fever and leukocytosis are common, and erythema multiforme[10] is often seen. Erythema nodosum was noted by Gans[11] in 10% of cases, usually occurring after operative interference in highly sensitized individuals. Meningeal symptoms, rheumatic manifestations[12] and enlarged spleen[13,14] occasionally occur.

The disease probably occurs with equal frequency in both sexes, clinical variations being due to differences of the lymphatic drainage of the male and female. In the male the primary lesion is usually in the coronal sulcus. The infection passes up the penile lymphatics (occasionally causing a lymphangitis) and usually becomes localized in the inguinal glands. Rarely, because of the meager lymphatic channels, the iliac and hypogastric glands are involved. Although the intrapelvic glands are but rarely penetrated in the male, Bloom[15] recently observed 3 cases of rectal stricture in men, out of a total of 7 cases. Elephantiasis of the male pudenda is occasionally seen.

The pathologic changes in the involved lymph nodes are probably not pathognomonic but are quite characteristic during the acute stages. They are not easily confused with tuberculosis, syphilis, Hodgkin's disease, sarcoma, or the more common infections of lymph nodes. The earliest change is the presence of multiple foci of epithelioid cells which may contain large giant cells. Many of these areas are transformed into micro-abscesses composed largely of neutrophils and large acidophilic mononuclear cells.[16] These may coalesce to form larger abscesses. The normal structure of the node is lost as the involvement progresses. The process frequently spreads to the periglandular tissues and sinus formation (often multiple) occurs with drainage of the abscesses. Secondary infection is then frequent and chronicity is nearly the rule. In a number of our cases in which the involved nodes were excised at an early stage, the pathologist has ventured a diagnosis of lymphopathia venereum from the appearance of the microscopic picture (Fig. 1).

In from 2 to 6 weeks after the onset of the adenopathy, an allergic reactivity of the body tissues develops, which is demonstrable in nearly 100% of cases by the intradermal reaction of Frei.[17] The antigen for this test is prepared from the pus obtained by aspiration of a bubo of a proven case of lymphopathia venereum. The technique for its preparation and administration is given in detail by DeWolf and VanCleve.[1] As the disease progresses the intensity of the reaction roughly parallels the severity of the involvement. In the latter manifestations, as will be pointed out in the present series, the reaction may decrease in intensity.

Frei believes that there are no false positive reactions. Cutaneous anergy occasionally occurs in active tuberculosis, in early florid syphilids, in high fever, in relapsing lymphopathia venereum lesions and sometimes in chancroid.[18]

In the female, inguinal adenitis is rarely seen, the virus usually passing to the intrapelvic glands. The anterior $\frac{2}{3}$ of the vulva is drained by the inguinal glands. The posterior $\frac{1}{3}$ is drained by the

FIG. 1.—Low-power photomicrograph of an inguinal lymph node excised during the acute stage of involvement by lymphopathia venereum. Note the multiple abscesses of variable sizes. High-power examination shows the abscesses to be made up largely of neutrophils and mononuclear cells with acidophilic cytoplasm. At the borders of the abscesses, which are quite irregular, a hyperplasia of the reticuloendothelial elements of the lymph node is evident and a number of giant cells are seen whose nuclei suggest reticuloendothelial origin.

intrapelvic glands, and there are extensive connections with the cutaneous lymphatic network of the anus. The vulvar and vaginal lymphatics have further ramifications to the anorectal glands, to those in the pouch of Douglas and to those lying in the broad ligament. The female, then, is subject not only to occasional inguinal involvement, but more commonly develops intrapelvic involvement with subsequent rectal stricture, perimetritis and perisalpingitis,[19]

esthiomene (vulvar elephantiasis), and perirectal granuloma and ulceration.

The exact pathogenesis of these later manifestations is not known. Frei believes that they are due to cicatricial contractions, to lymphatic blockage and to secondary infection. Barthels and Biberstein,[20] however, believe that active lymphopathia venereum is still present. They found a retrograde thrombotic lymphangitis with subsequent dilatation of the lymph spaces, characteristic stellate abscesses and inflammatory infiltrate. Their hypothesis of an attenuated virus has been in part proved by the recent experimental work of Ravaut.[21]

In the past a number of etiologic agents have been advanced as the causal factor in benign rectal stricture. Syphilis, tuberculosis, gonorrhea, chancroid and amebic dysentery have been most frequently suspected. The findings common to all of the large series of cases have been the high incidence of the condition in women (especially in the lower classes and the colored race), its occurrence during the period of greatest sexual activity (20 to 50 years), and the location of the stricture within a few centimeters of the anus.

In 1928 Frei and Koppel[22] reported the presence of a positive Frei test in 5 cases of rectal stricture. One case occurring in a male showed evidence also of an old involvement of the inguinal lymph nodes. Following this report many observers confirmed their findings. In this country Cole[2] reported the presence of a positive Frei test in all of 15 cases of anorectal syndrome and esthiomene. Concomitant or preceding perirectal abscesses, fistulæ and draining sinuses were frequent. In a series of 25 cases, all in negro women, Martin[23] noted a positive Frei test in 20 cases. Lee and Staley[24] in an excellent article on rectal stricture reported 16 cases of this condition (13 women and 3 men) 14 of whom had a positive Frei test.

The diagnosis in the male is usually easy. A positive Frei test is suggestive, but requires interpretation. Like the Wassermann reaction, it may be unrelated to the presenting lesion. Sarcoma, tuberculosis, gumma, lymphoblastoma and actinomycosis are most frequently confused. Specific treatment should be given if the Wassermann reaction is positive, but true cases of lymphopathia venereum often involute during antiluetic therapy.[25] Rectal stricture is rarely, if ever, syphilitic. Frei believes that it may occasionally be chancroidal or gonorrheal in origin.

Data. In this series 47 cases of lymphopathia venereum are presented, 22 males and 25 females. Forty (85%) were colored. These patients have been collected largely from the Out-patient Clinics, the annual total attendance of which approximates 22,500, with 37% colored. This suggests a much higher incidence of the disease in the colored race.

In 26 cases the disease was manifested by inguinal adenopathy. There were 22 males and 4 females; 22 colored and 4 white. The ages of the patients ranged from 17 to 45 years (average 25). The most common duration of the disease when first seen was from 2 to 4 weeks. Suppuration with sinus formation was rarely seen at this time. Four cases presented draining sinuses which had been present from 1 to 14 months. An evanescent primary lesion was seen on the penis in two instances. There was a history of a similar lesion in 1 other case. No clinical findings of chancroidal disease were found. Acute gonorrheal urethritis and lymphopathia venereum occurred simultaneously in 1 patient. The 4 women presented no evidence of rectal stricture but typical vulvar elephantiasis (esthiomene) was present in one instance. A positive Wassermann and Kahn test was obtained in only 2 of the 26 cases.

The Frei test was positive in all of the cases of inguinal adenopathy. In 5 cases of inguinal adenitis secondary to chancroidal lesions, and 4 cases secondary to acute gonorrheal urethritis, the Frei test was negative. It was negative also in 2 cases of granuloma inguinale, and 1 of reticulum cell sarcoma of the right groin.

There were 21 cases of rectal strictures, all occurring in the female, 18 in the colored race. The youngest patient was 19, the oldest 63 (average 37). The duration of symptoms when first seen, varied from 3 months to 9 years (average 4 years). The most frequent early symptom was an increasing constipation. Painful defecation, rectal bleeding, incontinence of feces, and discharges from the rectum were prominent features. In several cases there was a history of long standing draining sinuses about the anus. The location of the stricture was usually within 3 to 5 cm. of the external anal sphincter and within reach of the examining finger in all cases. This corresponds in location with the sites of the chief lymphatic networks about the anus and rectum (Fig. 2).

In 15 cases (71%) the Frei test was positive (strongly positive in 11 and moderately in 4). In the remaining 6 cases (29%) the Frei test was considered negative (there was a very slight reaction however in 3 of these 6 cases).

The Wassermann and Kahn tests were strongly positive in 5 of the 21 cases (23%). Four cases had both a positive Frei and a positive Wassermann reaction. Eleven cases had a positive Frei test and a negative Wassermann. Of the 6 cases with a negative Frei test, 1 had a positive Wassermann.

Three deaths occurred among the patients with rectal stricture. All of these cases had negative Frei tests. One case died as a result of a cerebral accident, followed by cardiac insufficiency and pneumonia. The blood Wassermann test was strongly positive, but at necropsy no pathologic evidence of syphilis was found. The rectal stricture began just inside the anus and extended upward a distance of 15 cm. The wall was fibrous and thickened and the mucosa was

congested. In some areas it was replaced by hemorrhagic granulation tissue.

In the second fatal case, death resulted from peritonitis which followed dilatation of the rectal stricture. At necropsy there was

FIG. 2.—Photograph of anus and rectum removed surgically in a case of benign rectal stricture. The patient was a colored woman aged 27. Increasing constipation with painful defecation had been present for 2 years. Bleeding from the rectum was frequent following straining at stool. A draining sinus which followed incision of a perirectal abscess, had been present for 6 months before removal. Clinically the stricture was located 4 cm. above the external anal sphincter and admitted only the tip of the forefinger. The Frei test was strongly positive (2 different antigens). Wassermann reaction was negative. The site of the stricture with ulceration of the mucosa of the lower rectum is evident. (Photograph after fixation which caused some shrinkage of the specimen.)

a large perirectal abscess, with extension upward along the left ureter to the perinephric tissues. The stricture was 5 cm. from the

external sphincter and associated with extensive ulceration of the rectum.

The third patient died also from a generalized peritonitis. Extreme emaciation and debility were present, with secondary anemia and typical skin lesions of pellagra. At necropsy the stricture was 3 cm. from the anus and extended upward a distance of 8 cm. Over this area, the mucosa was absent. The entire rectum and a portion of the sigmoid showed an acute ulcerative process, with the extension of the inflammation through the bowel wall to the peritoneal surface.

Microscopic sections from the stricture areas showed a marked fibroblastic proliferation with round-cell infiltration in all of these cases. In the latter 2 cases there was also acute inflammation present. In none was there evidence to suggest tuberculosis, syphilis or carcinoma associated with the stricture.

Treatment. There is no specific treatment for lymphopathia venereum. In those cases presenting inguinal adenitis surgical excision, Roentgen ray therapy and Frei antigen, intracutaneously, were all tried. Aspiration of the suppurating glands was frequently done when sinus formation was imminent. In a few cases incision and drainage were necessary. In general it seemed that sinus formation delayed recovery. Weekly injections of tartar emetic intravenously were used in several cases.

Three patients who failed to return for therapy were seen at a later date, and spontaneous regression of the inguinal adenitis had occurred without sinus formation. In view of this, and because of the poor follow up in the type of patient seen with this lesion, no conclusion can be drawn as to the results of therapy.

Tamura[5] has recently reported cultivation of the virus on a medium of Tyrode's solution to which guinea-pig tissue had been added. When the culture was heated and used as an antigen for the Frei test it gave positive results in proven cases of lymphopathia venereum and negative results in normal individuals without this infection. The use of the virus culture in treatment as suggested by Tamura, would seem to be a step toward specific therapy in this disease.

The treatment of rectal strictures, when fully developed, is a surgical problem. It is doubtful if an active lymphopathia venereum infection is present in most of these cases, the stricture probably being the result of the healing process, with marked fibrous tissue proliferation. During the development of the stricture, which probably requires a number of years, non-surgical therapy may be of value as the lymphopathia venereum infection may be present in an attenuated form.

In 1 of the cases of this series, a colored woman, aged 27, symptoms has been present for 18 months. Painful defecation was present with frequent passage of small amounts of blood. Purulent

discharge from the anus was usually present. During this time she had 2 "boils" about the anus, which ruptured spontaneously and drained for an indefinite period. During several weeks preceding the time the patient was first seen, rectal pain had been a prominent feature, being present nearly continuously and interfering with sleep. Weight loss was striking. Inspection revealed a small drainage sinus lateral to the anus. Rectal examination was excruciatingly painful. The sphincters were very spastic and just inside the anus a stricture was present, which just admitted the forefinger. This was present as far as could be reached, and tender to palpation. A sanguinopurulent discharge was present following the examination.

Two Frei tests were strongly positive. The blood Wassermann test was negative. On the supposition that active infection was still present, tartar emetic was given intravenously. Relief from pain occurred within a few days. When examined 1 week later, the tenderness and spasm were greatly diminished. After 6 weekly injections of tartar emetic the patient was practically free from symptoms. Objectively the stricture was unchanged.

Comment. It is generally stated that the Frei test should be read after an interval of 48 hours. The possibility of a delayed positive reaction should be kept in mind. In 3 of the present series the Frei test did not become positive until after 72 hours. It would seem that the Frei test is best read on the 4th or 5th day. By this false positive reactions will have subsided.

In 4 instances of rectal stricture the Frei test was only moderately positive, in 3 there was a minimal reaction and in 3 there was no reaction (using 2 different antigens). It may be that in some of these long-standing cases there is a diminution in the intensity of the reaction and it is possible that the Frei test may occasionally become negative. On the other hand strongly positive reactions are often present many years after the infection has subsided. In those cases with a negative Frei test there was no history to suggest a previous gonorrheal or chancroidal infection. However, it is difficult to rule out these two infections as etiologic factors in the production of rectal stricture.

It would seem advisable that all cases of perirectal abscesses and fistulæ in ano of unknown etiology should receive a Frei test. All contacts of cases in which the infection is active should be similarly tested.

The fact that the average age of the patients with rectal strictures was 37 years as compared to 25 years in those cases with inguinal adenopathy suggests that several years time is necessary for the development of the former lesion.

Summary. 1. Of 47 cases of lymphopathia venereum infection here reported, 26 presented inguinal adenopathy and 21 rectal stricture. One case was complicated by esthiomene.

2. Lymphopathia venereum occurs with much greater frequency in the colored race.

3. Reading the Frei test after the 4th day is recommended.

4. The possibility of a diminution or absence of the Frei reaction in long-standing cases is considered.

5. All patients with inguinal adenopathy of obscure etiology and those with rectal stricture should be tested with Frei antigen.

6. Cases presenting perirectal abscesses, fistulæ in ano, or obscure pelvic infections should also be tested to eliminate the possibility of a lymphopathia venereum infection as an etiologic factor.

7. There is no specific treatment for the disease. Various methods have been considered.

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STUDIES IN HYPERTENSION.

1. THE PRODUCTION OF EXPERIMENTAL HYPERTENSION AND A CORRELATED EFFECT UPON THE NITROGEN DISTRIBUTION OF THE BLOOD PROTEINS.

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IN a preliminary report[1] upon the production of experimental hypertension in rabbits by the injection of various substances, it was noted that of the amino acids employed, aspartic acid alone consistently produced hypertension. Our study has been continued using a large number of animals with the object of noting the effect of some of the supposed etiologic factors, which from clinical observation in man, are assumed to be associated with hypertension. No attempt will be made in the present paper to summarize, even briefly, the many views and experimental investigations on the problem of hypertension which the literature of the past quarter of a century records.

In accordance with the idea expressed above, chronic nephritis was produced in one group of animals; in another group the effect

of lipoids was observed and in a third the results of repeated injections of various amino acids was investigated.

Procedure. The following standard routine was adopted. Upon receipt of the rabbits, they were permitted to rest for 2 weeks. During this and for the entire period of observation, they were placed on a standard diet of carrots, oats and greens, such as beet tops, lettuce, etc. Blood pressure determinations were made 3 times weekly during the entire life of the animal, the method of McGregor[2] being employed, and 4 or 5 readings taken at each examination. The average of these readings was recorded. The diastolic pressure was not taken. The instrument used was a mercury manometer and all the readings were made by the same individual. It was found that after the animals had their pressures taken 2 or 3 times, they no longer became excited and remained perfectly quiet while restrained on the board. Urine examinations were made 3 times a week during the entire study and determinations of the blood urea nitrogen and creatinin were made during the 2 weeks control period and at intervals thereafter. All animals showing a systolic blood pressure of 120 mm. Hg or over during the control period were discarded.

Control Observations. In 66 normal rabbits the systolic blood pressure varied between 92 and 118 mm. Hg; in 19 (25.7%) the pressure varied between 92 and 100 mm., in 39 (59.1%) between 100 and 110 mm. and in 8 (15.1%) between 110 and 118 mm. Hg. In McGregor's[2] series of 84 normal rabbits, the averaged systolic blood pressure was 125 mm. Hg with a normal variation of 20 mm. Hg. In a number of control animals not included with the above mentioned 66 animals, spontaneous hypertension to a varying degree was observed. The observation period of the group was between 6 and 41 weeks and the actual rise of blood pressure varied between 24 and 49 mm. Hg.

Nephritis with Hypertension. Uranium nitrate was used to produce a nephritis, only 3 animals surviving sufficiently long to make the observations of any value. Two animals survived for 42 weeks. One animal received 88 doses of uranium nitrate, each dose being 0.7 mg., while the second received 84 doses of 0.58 mg. In both animals albumin and casts appeared in the urine and in both there was marked nitrogen retention in the blood, the blood urea nitrogen being 41.6 and 42.3 mg. per 100 cc. respectively. The blood pressure in the first animal rose from 110 to 132 mm. Hg and in the second from 108 to 155 mm. Hg. The third rabbit survived but 5 weeks and received 10 doses of 0.58 mg. of uranium nitrate. Albumin and casts appeared in the urine, the blood urea nitrogen rose to 63.3 mg. per 100 cc. and the blood pressure rose from 103 to 129 mm. Hg. Histologic examination of the viscera showed the usual picture of a uranium nephritis which was progressing to a chronic interstitial type. There was no evidence of vascular sclerosis.

It is evident, even in this small group, that a nephritis induced by repeated small doses of uranium nitrate causes an increase of the systolic blood pressure in rabbits.

Hypertension and Blood Lipoids. It has been maintained by some that hypercholesterolemia can be demonstrated in certain cases of hypertension and that there is an etiologic relationship. In accord-

FIG. 1.—Glomerular nephritis after injection of aspartic acid.

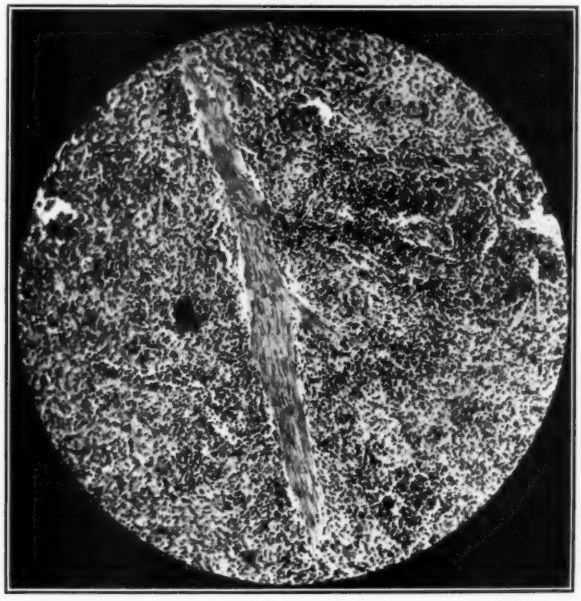

FIG. 2.—Splenitis after injection of aspartic acid.

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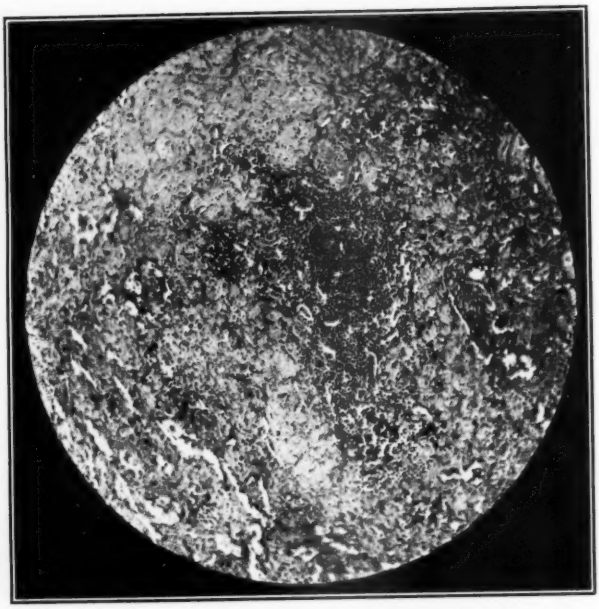

FIG. 3.—Spleen after injection of aspartic acid.

ance with this viewpoint a group of 7 rabbits were injected with repeated doses of cholesterol and 1 with a combination of cholesterol and lecithin. Of this group 5 animals survived.

The statistical data of the group are given in Table 1. With the exception of 1 animal, in which albumin and casts were found in the urine during the last month of life, no pathologic changes were observed in either the urine or blood.

As shown in Table 1, the repeated injection of cholesterol was followed by a mild degree of hypertension. In 1 animal when cholesterol and lecithin were combined, the hypertension did not develop. However, when the same quantity of cholesterol was administered alone to the animals, an increase in blood pressure was produced.

Since it has been shown that large doses of viosterol may upon occasion produce sclerotic changes in the vascular system, this substance was also tried, the data being grouped with the lipoids since chemically viosterol is a sterol (Table 1). It will be noted that a mild degree of hypertension did develop, always associated with kidney damage, but without nitrogen retention.

TABLE 1.—BLOOD PRESSURE IN CHOLESTEROL AND VIOSTEROL INJECTED RABBITS.

Animal No.	Period of observation (in weeks).	No. of doses.	Amount, mg.	Substance injected.	Blood pressure control period.	Blood pressure averages month by month.*
63	12	8	500	Cholesterol	109	128–130–**133**
62	10	4	500	Cholesterol	116	**133**–130–121
32	42	18	500	Cholesterol	111	116–128–**143**–138–141–138–136–124–123–114
61	34	7	500 100	Cholesterol Lecithin	117	**140**–136–131–134–121–112–111–103
88	23	61	200	Cholesterol	99	113–**116**–107–100–100–102
42	5	25	1 cc.	Viosterol 250 D	107	**113**
43	10	48	1 cc.	Viosterol 250 D	99	100–**109**–100
44	31	99	1 cc.	Viosterol 250 D	108	108–112–118–124–**126**–115–118–112
45	23	96	1 cc.	Viosterol 250 D	97	105–115–125–**130**–130

* The highest pressure obtained is in bold type.

Protein Putrefaction Products. Two protein putrefaction products, putrescin and tyramin, were used in another group of rabbits. Only 2 animals survived sufficiently long to make the observations of any value. One animal during 27 weeks received 86 injections of 100 mg. each of putrescin. The lowest blood pressure recorded was 105, the highest 123. The second animal during 11 weeks received 60 injections of 50 mg. each of tyramin. The lowest blood pressure recorded was 107 and the highest 110. In both animals the urine and blood chemistry were normal.

As far as can be judged from these few observations, it seems that neither putrescin nor tyramin when injected into rabbits produce any rise in blood pressure.

Amino Acids. In another group of animals various amino acids were injected. Since many of the experimental results were negative and the survivors few, the statistical data are given without comment (Table 2).

TABLE 2.—BLOOD PRESSURE AFTER INJECTION OF AMINO ACIDS.

Period of observation (in weeks).	Substance injected.	Number and amount per injection.	Blood pressure.	
			Minimum.	Maximum.
10	Histidin	40–100 mg.	107	113
23	Tryptophane	29–200 mg.	106	121
27	Tyrosin	51–100 mg.	105	115
33	Asparagin	82–200 mg.	112	121
33	Asparagin	28–240 mg. 46–200 mg.	108	122
19	Asparagin	40–200 mg.	104	134
18	Glutamic acid	94–500	109	122
17	Glutamic acid	44–100	105	129
44	Glutamic acid	117–100	122	141

Aspartic Acid. Since it is in this group that a significant increase in blood pressure was found, detailed discussion of all of the 11 surviving animals will be presented (Table 3).

In practically all of the animals of this group, albumin and casts appeared in the urine within 4 to 6 weeks after the first injection. The amount of albumin was never more than a faint trace and in none of the animals was there nitrogen retention in the blood. This is analogous to the condition commonly found in essential hypertension in man, where the only symptoms often are increased blood pressure with or without albuminuria and no nitrogen retention in the blood.

At autopsy the kidney lesion found in these animals was that of a glomerular nephritis with congestion of the tufts and an exudate in the glomerular space (Fig. 1). If one were to express the extent of the lesion mathematically, it would be in the general order of one glomerulus out of 15.

In the spleen a series of changes occurred which led to almost complete fibrosis of the organ. In extreme cases the usual histology of the organ was completely replaced by a mass of hyalin connective tissue in which small foci of round-cell infiltration were demonstrable. For the greater part the sinuses were still preserved, though the lymphoid structures were completely destroyed. The best histologic description of the advanced stages is that the sections could not be recognized as spleen. These changes in the rabbit spleen have their counterpart in man, where in cases of hypertension chronic splenitis in varying degrees is also observed, none, however, as extensive as that observed in the rabbit. The condition of the spleen is shown in Figures 2 and 3.

TABLE 3.—BLOOD PRESSURE AFTER INJECTIONS OF ASPARTIC ACID.

Animal No.	Period of observation	Weight.	Aspartic acid.		Blood pressure in mm. Hg.																					
			No. of injections	Amount.	Control period.	Monthly average.																				
	Weeks.	Grams.		Mg.		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
92	17	1895	89	500	102	116	130	135	131	127																
51	19	1689	12 38	80 160	100	116	145	150	158	167																
67	16	1655	46	200	115	138	153	159	160																	
33	26	2145	22 49	40 120	99	112	114	137	145	161	160	150														
93	38	1988	128	500	101	113	126	123	126	132	115	120	124	131												
31	21	2097	17 68	40 120	105	108	127	145	154	163	169															
87	45	1995	180	500	105	109	126	123	128	127	124	118	117	115	119	125										
40	85	2216	21 63	40 120	100	110	130	135	145	151	153	134	137	124	125	112	115	117	127	119	128	129	118	128	124	129
86	26	2090	164 23 10	100 200 500	97	109	121	128	127	125																
118	17	2130	121 50	500 500	105	127	141	134	145																	
120	16	2090	30	500	102	119	133	145	156																	

Sections of the great vessels showed no definite histologic change, except for a possible increased prominence of the elastic fibers and occasional areas of vacuolization in the media. There were two exceptions: Rabbit 87 showed definite calcified areas in the aorta, and Rabbit 33 showed marked sclerosis of the tibial vessels associated with gangrene of all the toes on the hind legs leading to spontaneous amputation.

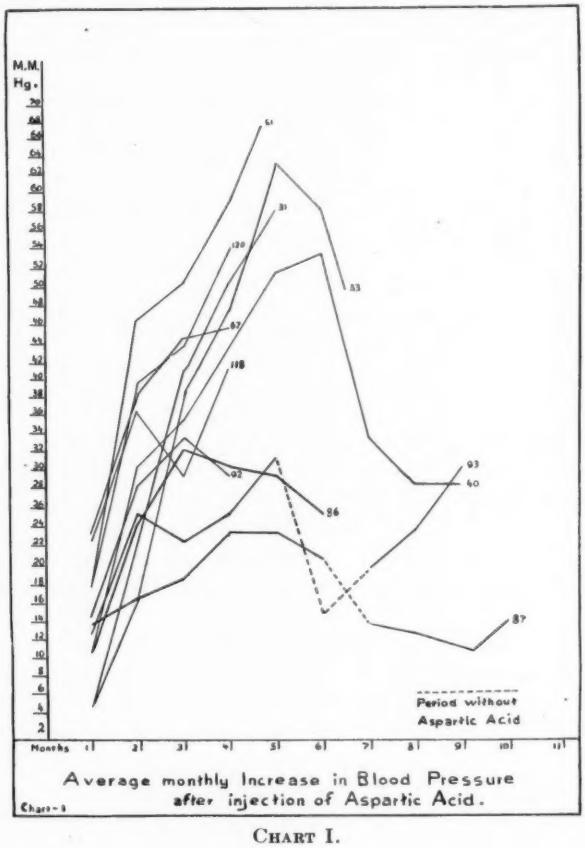
M.M. Hg.
Months
Period without Aspartic Acid
Average monthly Increase in Blood Pressure after injection of Aspartic Acid.

CHART I.

The blood pressure of the rabbits injected with aspartic acid showed a definite continuous rise from month to month in practically all of the animals (Chart I). The rise was more marked in some animals than in others. Allowing for seasonal variations, similar changes were not observed in the control animals, nor in animals injected with other substances. While the period of observation extended from 4 to 21 months, the data for only 10 months is shown graphically. The rise in pressure is slow, increasing from 4 to 23 mm. Hg in the first month. The maximum increase was

obtained in 2 animals in 3 months, in 3 animals in 4 months, in 5 animals between 4 and 5 months and in 1 animal in 6 months.

When injections of aspartic acid were temporarily discontinued for a period, as in Animals 87, 93 and 40, there was a definite decline in the blood pressure, but upon resumption of the injections the pressure resumed its upward trend.

Having noted that the repeated injections of aspartic acid produced a rise in blood pressure, the more immediate effects of a single injection were studied in 2 instances. The blood pressure was taken 1, 6 and 24 hours after an injection of 500 mg. The increase in blood pressure of the first animal at the designated intervals was 6, 12 and 6 mm. Hg, and in the second animal it was 4, 2 and at the last interval a drop of 8 mm. Hg below the original level. These changes are within normal limits of variation and can be discarded.

In Chart II we have plotted the blood pressure curves of Rabbits 87 and 40 week by week for the entire period of observation.

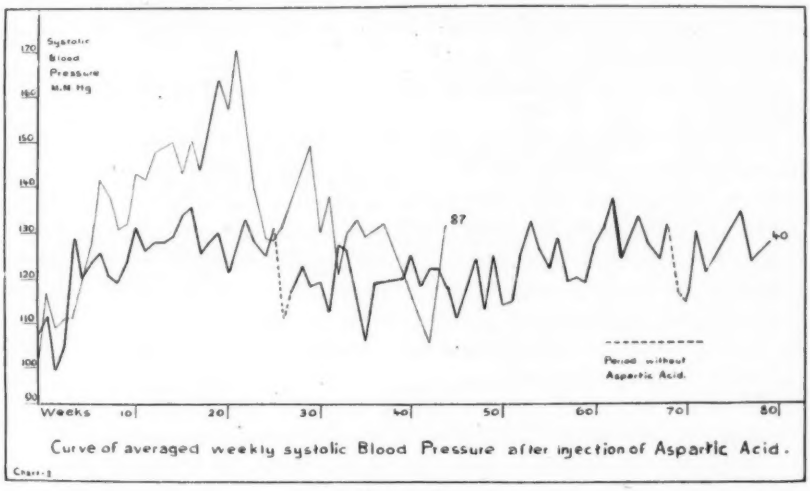

CHART II.

Guanidin Carbonate. Major[3] and his coworkers have reported an increase of guanidin in the blood in cases of hypertension in man. This substance was injected into another group of rabbits, of which 5 survived. In all of the animals a nephritis of varying severity was found postmortem, and during life albumin and casts were found in the urine. There was no evidence of nitrogen retention in the blood.

This group of animals was under observation from 6 to 26 weeks. The control blood pressures varied between 94 and 117 mm. Hg. All of the animals received between 13 and 32 injections of 200 mg. of guanidin carbonate and the maximum blood pressure during the experimental period ranged between 129 and 172 mm. Hg.

A similar type of fibrosis of the spleen observed in the aspartic acid hypertension was also noted in this group.

It is evident that injections of guanidin carbonate are followed by the development of hypertension. Attention is called to the fact that guanidin carbonate is toxic and gangrenous areas developed at the site of injection. The periods of observation were short due to the high mortality, as compared to the aspartic acid group.

Succinic Acid. In this group 3 animals survived; diarrhea and abscesses at the site of injection were common. The blood pressure before injection varied between 100 and 103 mm. Hg. They were under observation from 15 to 36 weeks. One animal received 115 injections of 50 mg. of succinic acid, the second 37 injections of 100 mg., and the third 135 injections of 100 mg. The rise in blood pressure during the experimental period was not sufficient to be of significance.

In all of the animals a nephritis of slight severity was observed postmortem, and during life all showed albumin and casts. There was no nitrogen retention in the blood. A slight fibrosis of the spleen was also observed.

The injection of succinic acid into rabbits does not produce hypertension.

Nitrogen Distribution of the Blood Proteins. As part of the investigation, a study of the nitrogen distribution of the blood proteins of normal and hypertensive rabbits was undertaken, the results of which are recorded in this paper. The examinations deal with the distribution of the total, the amid, the hydrolyzable, the basic amino and the monoamino nitrogen of the whole blood, of the red cells and of the serum proteins from the same specimen of blood in normal rabbits and those made hypertensive by the repeated injections of aspartic acid.

All of the blood specimens were obtained in the morning, all food having been removed from the cages the previous evening. The technical methods for the analysis of the blood proteins have been described in detail.[4,5]

Normal Values: Table 4 records the total, the amid, the hydrolyzable, the basic amino and the monoamino nitrogen of the whole blood, red cells and serum proteins of 17 normal rabbits. To conserve space, only the high, low and the average for each of the constituents are given. The animals varied in weight from 1507 to 2755 gm.

Special attention is directed to the serum proteins and emphasis is placed on the basic amino (subsequently termed B.A.N.) and monoamino nitrogen (subsequently referred to as M.A.N.). We have proposed a ratio of the monoamino and the basic amino nitrogen which will be referred to throughout this paper as the M/B ratio.

Changes in the amid nitrogen are of no significance. Neither this

fraction nor the humin nitrogen play a rôle in the results obtained since both are removed before the other fractions are determined. The humin nitrogen has not been reported in the tables. Reference to these two fractions will, therefore, be omitted from the discussion.

TABLE 4.—NITROGEN DISTRIBUTION OF THE WHOLE BLOOD, RED CELLS AND SERUM PROTEINS IN 17 NORMAL RABBITS.

	Total N.	Amid N.	Total N[1] after hydrolysis.	Basic amino N.	Total N. % after hydrolysis.	Total N. of phosphotungstic acid filtrate.	Monoamino N.	Total N. % after hydrolysis.	M/B ratio.
				Milligrams per 100 cc.					
				Whole blood					
High	2670	220	2420	700	31	1770	1620	76	4.2
Low	2005	60	1560	360	17	1160	1000	54	1.8
Average	2391	107	2060	535	25	1520	1340	65	2.6
				Red blood cells					
High	2040	140	1870	530	34	1350	1220	74	4.2
Low	970	30	700	160	18	850	740	48	1.6
Average	1717	86	1491	409	27	1096	959	65	2.5
				Serum proteins					
High	900	80	670	170	25	510	500	82	5.5
Low	570	17	460	90	15	340	270	47	2.3
Average	669	27	548	117	21	428	370	66	3.2

[1] After removal of humin and amid nitrogen.

In normal rabbits the basic amino nitrogen of the serum proteins varied between 90 and 170 mg. with an average of 117 mg., forming between 15 and 25% with an average of 21% of the total nitrogen after hydrolysis. The monoamino nitrogen varied between 270 and 500 mg. with an average of 370 mg. per 100 cc. The percent which this fraction formed of the total nitrogen after hydrolysis varied between 47 and 82 with an average of 66. The M/B ratio varied between 2.3 and 5.5 with an average of 2.3. In 16 rabbits the ratio varied between 2.3 and 3.9 and in only 1 animal was the ratio at the high point of the extremes.

Nitrogen Distribution in Hypertension. Since significant changes occur in the serum proteins of hypertensive animals, discussion will be confined entirely to this fraction. The data presented in Table 5 shows the nitrogen distribution of the serum proteins of rabbits before and after the production of hypertension with aspartic acid and guanidin carbonate. A more detailed discussion of some of the results follows.

Protocols. *Rabbit 92.* During the control period the blood pressure was 102. (In the following portions of the report, mm. of Hg will be omitted from the blood pressure values and mg. per 100 cc. will be omitted after the values of the various nitrogen fractions. The percentage values in parenthesis indicate the percentage of that particular fraction of the total nitrogen after hydrolysis.) At the same period the B.A.N. was 90 which

TABLE 5.—NITROGEN DISTRIBUTION OF THE SERUM PROTEINS IN RABBITS WITH HYPERTENSION.

Rabbit.	Blood pressure.	Total N.	Amid N.	Total* N. after hydrolysis.	Basic amino N.	Total N. % after hydrolysis.	Total N. of phospho-tungstic acid filtrate.	Mono amino N.	Total N. % after hydrolysis.	M/B ratio.	Substance injected.
	Mm. Hg.	Milligrams per 100 cc.					Milligrams per 100 cc.				
92	102	804	25	600	90	15.0	500	490	82.0	5.5	Control
92	130	610	20	590	33	5.6	550	530	90.0	16.0	Aspartic acid.
93	90	620	21	540	110	20.4	450	400	74.0	3.6	Control.
93	130	530	20	470	40	8.5	430	450	96.0	11.2	Aspartic acid.
93	130	850	21	630	30	4.7	600	600	95.2	20.0	Aspartic acid.
93	114	680	27	510	140	27.4	370	300	60.0	2.1	Aspartic acid discontinued 3 weeks.
118	105	650	30	530	130	24.5	400	370	70.0	2.8	Control.
118	130	600	10	570	70	12.2	500	500	88.0	7.1	Aspartic acid.
120	102	610	20	550	130	23.6	420	420	76.0	3.2	Control.
120	144	620	20	490	70	14.3	420	420	86.0	6.0	Aspartic acid.
98	104	900	22	530	130	24.7	400	300	55.5	2.3	Control.
98	128	780	22	390	40	10.0	350	340	87.0	8.4	Guanidin carbonate.
103	106	800	40	500	100	20.0	400	350	70.0	3.5	Control.
103	136	800	40	500	70	14.0	440	350	70.0	5.0	Guanidin carbonate.
103	118	810	40	710	140	20.0	570	300	42.0	2.1	Guanidin carbonate discontinued 1 month.

* After removal of humin and amid N.

represented 15% of the total nitrogen after hydrolysis, the M.A.N. was 490 (82%) and the M/B ration was 5.5. The blood pressure reached a maximum of 150, a rise of 48, 106 days after the first injection of aspartic acid. During this period 78 injections of 500 mg. of aspartic acid were given. Five days later the pressure was 130 and on that day the serum proteins were B.A.N. 33 (5.6%), M.A.N. 590 (90%), and the M/B ratio 16.0. During the period of hypertension a change in the distribution of the nitrogen fraction had occurred. The important change is a decrease in the B.A.N. and an increase in the M.A.N. with a consequent rise in the M/B ratio. Attention is called to this fact since exactly similar changes have been observed in a group of cases of hypertension in man and will be reported in a subsequent paper.

Rabbit 93. During the control period this animal had a blood pressure of 90 and the B.A.N. was 110 (20.4%), the M.A.N. 400 (74%), and the M/B ratio 3.6. After 79 injections of 500 mg. of aspartic acid in 108 days the blood pressure rose to 130. At this time the B.A.N. was 40 (8.5%), the M.A.N. 450 (96%) and the M/B ratio 11.2. Sixteen injections of 500 mg. of aspartic acid were given in the ensuing 35 days, the blood pressure rising to 144. The B.A.N. was 30 (4.7%), the M.A.N. 600 (92.5%) and the M/B ratio 20.

Injections of aspartic acid were discontinued for 25 days, at the end of which time the blood pressure was 114. At the same interval the B.A.N. rose to 140 (27.4%), the M.A.N. fell to 300 (60%) and the M/B ratio fell to 2.1. The results in this instance demonstrated that blood pressure, monoamino nitrogen and the M/B ratio rose after the repeated injections of aspartic acid and that a discontinuance of the injections was followed by a more or less complete return to the normal.

Rabbit 118. During the control period the blood pressure was 105, the B.A.N. 130 (24.5%), the M.A.N. 370 (70%) and the M/B ratio 2.8. Over a period of 64 days, 24 injections of 500 mg. of aspartic acid were given with blood pressure to 152. Some days later the blood pressure had fallen to 130 and the B.A.N. was 70 (12.2%), the M.A.N. 500 (88%) and the M/B ratio 7.1.

Rabbit 120. During the control period the blood pressure was 102, the B.A.N. 130 (23.6%), the M.A.N. 420 (76%) and the M/B ratio 3.2. In 63 days this animal received 12 injections of 500 mg. of aspartic acid. The blood pressure was then 144, the B.A.N. 70 (14.3%), the M.A.N. 420 (86%) and the M/B ratio 6.0. In this animal there was no actual increase in the amount of monoamino nitrogen, but the percentage of this fraction of the total nitrogen after hydrolysis was increased. The rise in the M/B ratio was due to a fall in the B.A.N.

Rabbit 98 was observed for 6 weeks, receiving 24 injections of 200 mg. of guanidin carbonate. During the control period, the blood pressure was 104, the B.A.N. 130 (24.7%), the M.A.N. 300 (55%) and the M/B ratio was 2.3. Forty days after the first injection the blood pressure was 152, the B.A.N. 40 (10%), the M.A.N. 340 (87%) and the M/B ratio 8.4.

Rabbit 103. This animal was observed for 20 weeks and received 21 injections of 200 mg. of guanidin carbonate. During the control period the blood pressure was 106, the B.A.N. 100 (20%), the M.A.N. 350 (70%) and the M/B ratio 3.5. When the pressure had risen to 136, the B.A.N. was 70 (14%), the M.A.N. did not change, but the M/B ratio was 5. The injections were discontinued and 4 weeks later all of the nitrogen values and the M/B ratio were within normal limits.

Discussion. Clinical observation has indicated a relationship between hypertension and a variety of clinical entities; thus, chronic nephritis, chronic lead poisoning, syphilis and the excessive use of

alcohol are commonly regarded as important etiologic factors. There are also other conditions which are supposed to initiate or to keep the process in continuance and it seems logical to suppose that all these agents act through a common mechanism. It is also evident that this mechanism is intrinsic rather than extrinsic. Many have assumed that hypertension is due to a disturbance of metabolism, although just what processes are involved have never been definitely shown. The physiologic action of amino acids resulting from catabolism of proteins, or products resulting from failure of the organism to properly deaminate amino acids, might play some rôle in hypertension. It has been shown by the present experiments that aspartic acid, one of the normally existing amino acids in the organism, when repeatedly injected into rabbits produces hypertension and glomerulonephritis. This effect is not due solely to the presence of the amino group, since the injection of other amino acids does not produce hypertension. Glutamic acid which is closely related chemically to aspartic acid does not raise blood pressure. Aspartic acid and glutamic acid are two common monoamino dicarboxylic acids and differ from each other by one methyl group.

Deamination of amino acids is a property of a great many tissues of the body and it is probable that certain of them possess a selective action in this respect. Under normal conditions, presumably all of the amino acids in excess of the required nitrogenous structural units are deaminized, yet it is possible that with a perfectly normal mechanism for deamination, the organs cannot deaminize the aspartic acid at the rate at which it accumulates and there is an excess which is sufficient to cause an elevation of blood pressure. Deamination of aspartic acid results in the formation of succinic acid. Our experiments indicate that succinic acid plays no rôle in the production of hypertension.

The exact mechanism by which the blood proteins are formed from ingested amino acids is not entirely known and it is likely that the presence of a large quantity of any particular amino acid might alter the composition of the proteins, with resultant changes in their physical and chemical properties. In rabbits developing hypertension after the administration of aspartic acid, changes in the nitrogen distribution of the serum proteins occur. These changes are a lowering of the basic amino nitrogen values and an increase in the monoamino nitrogen fraction, in consequence of which there is a rise in the M/B ratio. Aspartic acid and glutamic acid are the principal amino acids which constitute the monoamino nitrogen fraction of the serum proteins. Since glutamic acid plays no rôle in the production of hypertension, it seems logical to assume that aspartic acid is the responsible factor.

Guanidin carbonate is not an amino acid, but it also is a hypertension producing agent, inducing changes in the nitrogen fractions

of the serum proteins of the same character as that observed after the injections of aspartic acid. In the guanidin animals the changes are more pronounced in the basic amino nitrogen fraction with little or no change in the monoamino nitrogen fraction. The M/B ratio of the guanidin injected animals is not as high as those of the aspartic acid group.

Conclusion. 1. Uranium nitrate when injected in small doses into rabbits produces nephritis with hypertension.

2. Cholesterol similarly administered produced a mild hypertension, while in a single experiment cholesterol and lecithin did not.

3. Of the amino acids injected, aspartic acid alone produces definite hypertension. At autopsy, the renal lesions of glomerulonephritis were found.

4. The aspartic acid hypertension in rabbits is not dependent upon the presence of the amino or dicarboxylic group.

5. Guanidin carbonate also produces hypertension when injected into rabbits.

6. A marked fibrosis of the spleen was observed in all of the animals which developed hypertension after the injection of aspartic acid.

7. The total, the amid, the hydrolyzable, the basic amino and the monoamino nitrogen distribution of the whole blood, of the red cells and of the serum proteins from the same specimen of blood have been determined in 17 normal rabbits and in 6 rabbits with hypertension.

8. In rabbits in which hypertension has been produced by the injection of aspartic acid, the basic amino nitrogen fraction of the serum proteins is decreased, the monoamino nitrogen fraction is increased and there is a rise in the M/B ratio.

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HEREDITARY ONYCHIAL DYSPLASIA.

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The anomaly presented in this article is not common, if a review of the literature may indicate its frequency. Nevertheless the subject is of unusual interest, and thus far, there seems to be no agreement as to the explanation of the method of inheritance in this syndrome. One might even gather that various writers were presenting different syndromes. Such, I feel, is not the case, and the most recent paper of Aschner,[1] in which an attempt is made to advance the theory that chance linkage of separate factors accounts for the syndrome, does not seem to offer an adequate solution to the problem.

Realizing the difficulties in explaining the genesis of this syndrome, the writer has presented the views of MacArthur,[2,7] with which he agrees, as the basis for much of the discussion which follows.

A case is presented as a typical example. The patient was admitted to hospital as a diagnostic problem. The history, other than dealing with the syndrome presented, will be but briefly mentioned.

Case Report.—G. S., a white male, aged 29, fisherman, English, single, was admitted to hospital on July 18, 1934, complaining of cough, and sputum. His past history was irrelevant. His family history was negative except for the peculiar dystrophy of nails which occurred in several instances. One female cousin is a patient in a hospital for mental diseases, who also shows the nail dystrophy. The functional inquiry was negative except for cough and sputum.

Physical examination showed few positive findings. The patient was intelligent, and coöperated well. He was well developed. The skin was normal over the whole body, except for scales over the elbows and knees, as one would expect to find in a salt-water fisherman. There was no obvious postural deformity, nor external evidence of any glandular disturbance. The hair was plentiful, and of medium texture; the scalp was clean. The eyes, ears, nose, mouth and throat were normal. The thyroid gland was normal in size and consistency. The trachea was in the midline. The right lung was normal. The left lung exhibited medium râles below the 6th rib, anteriorly, and the 9th rib, posteriorly, along with some dullness to percussion. There was nothing abnormal in the entire cardiovascular system. The systolic blood pressure was 110 mm. Hg, disatolic, 60. The abdominal muscular development was pronounced. There was a slight inguinal hernia on the left side. The genitalia were normal. The extremities showed no abnormal protuberances. The patellæ were normal in size and position. There was normal movement in all joints. The fingers and toes showed peculiar distribution of the nail substances (Figs. 4 and 5). The nail deficiency was most marked on the thumbs and great toes. These findings are very similar to those previously reported, and almost identical

FIG. 1.—Roentgen ray of hands shows unusual tapering of distal phalanges with spatulated tips. Arrows are drawn to show the changes. Injuries to the distal phalynx of thumb on right hand and little finger on left hand are evident. (Roentgen ray read by Dr. S. Kirkland, roentgenologist, Saint John General Hospital.)

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FIG. 2.—Roentgen ray of feet. There is unusual tapering of the distal phalanges with spatulated tips. The arrows drawn point out the defects. (Roentgen ray read by Dr. S. Kirkland, roentgenologist, Saint John General Hospital.)

with that of the female cousin mentioned. The spine and nervous system showed no abnormalities.

Laboratory data were as follows: Urine, normal. Blood, red blood cells, 5,730,000 per c.mm., with 88% hemoglobin; the white blood cells were 5000 per c.mm., with neutrophils 53%, eosinophils 2, lymphocytes 38, and monocytes 7. The blood Wassermann and Kahn tests were negative.

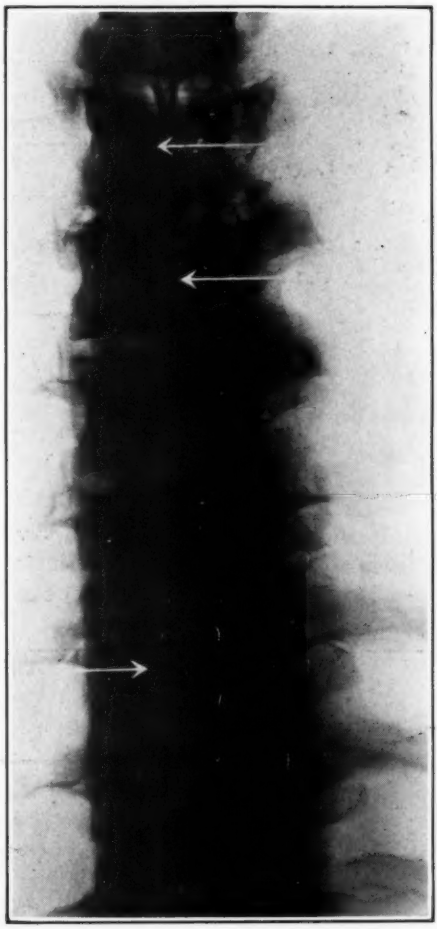

FIG. 3.—Roentgen ray of dorsal spine. This shows lateral wedging of the ninth dorsal vertebra, with some slight changes from normal in several other bodies (see arrows). (Roentgen ray read by Dr. S. Kirkland, roentgenologist, Saint John General Hospital.)

Roentgen ray of chest showed evidence of some bronchiectasis at the base of the left lung. Practically the entire skeleton was Roentgen rayed. This revealed some slight abnormalities of the hands, feet and dorsal vertebræ. The distal phalanges of the hands and feet were tapered and spatulated (Figs. 1 and 2). Lateral wedging of the dorsal vertebræ was also

evident (Fig. 3). The gradation of nail dystrophy is shown in photographs (Figs. 4 and 5).

FIG. 4.—Photograph of hands of G. S. The gradation of nail dystrophy is shown. There is no normal nail substance present. Thickening with heaping up and longitudinal furrowing is present. The shortening of the thumb on the right hand and little finger on the left hand are due to injuries.

Discussion. The family tree (Chart I) is composed of 35 members among whom nail dystrophy occurred in 11 instances. Unfortunately G. S., and a female cousin, mentally deficient, were the only

FIG. 5.—Photograph of feet of G. S. The distribution of nail substance is much the same as shown in the hands. No nails are normal.

individuals examined. Arrangements could not be made to get Roentgen films of the latter. The others were reached by a ques-

tionnaire, worded to reveal obvious defects such as alopecia, ichthyosis, absence of sweat glands, etc. Dystrophy of the nails was the only ectodermal abnormality reported, although the changes noted varied considerably. Several had difficulty in picking up small objects, due to lack of nail substance. No skeletal deformities were noted, and those present in G. S. were unlike any previously reported. Hypothyroidism has been suggested as a causative factor but no evidence of this was found in any member. As it is unlikely that this factor is of any importance in this syndrome, a basal metabolic rate was not done. One case of mental disease occurred in this family, but no conclusions can be drawn from this fact. The defects occurred in approximately one-half to one-third of the number of children whose parent was affected, and in no instance did an un-

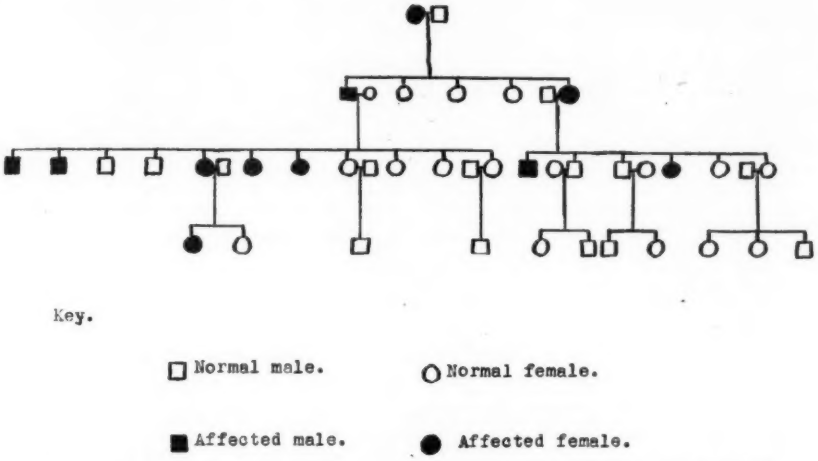

CHART I.—Family tree. There are 35 members. The symbols indicate nail dystrophy.

affected parent transmit a defect. Both sexes were equally affected. These findings are substantiated by those of Tobias.[3] Jacobson,[4] Thompson,[5] and Turner.[6] No marriage occurred between 2 affected individuals, nor have any such been reported. Consequently all cases are probably heterozygous (Dd). The possibility should be kept in mind that if any (DD) progeny, they might be lethally affected. It is safer then to admit that the gene (D) may not be dominant as at first seems probable.

Hereditary dystrophy of the nails has been reported associated with ectodermal and mesodermal defects and as an entity. Many had no Roentgen rays taken, and anomalies of the osseous system have undoubtedly been missed, as deformities are often revealed by this examination alone. The case presented here is an example of this. The gradation of nail dystrophy and other ectodermal and

mesodermal defects reported have varied greatly. It is probable that in most cases, at least 2, and possibly all three primary body layers are affected in this syndrome. Endodermal structures inaccessible to examination may also be involved. It is likely that the many clinical pictures met with are merely variations of the same disease. The case presented here is an example of the minor effects of the syndrome, while those showing such defects as absence of the patellæ, subluxation of the radius, etc., illustrate its more serious forms. If this assumption is correct, a satisfactory explanation of the genesis of this syndrome has not appeared thus far. The associated characters of the syndrome; the difference in its make-up in different families; its frequent dissociation, and its great variability among individuals are the chief unsolved genetic problems. Previous writers have attempted to account for these peculiar hereditary features by assuming either one or more modifying genes (Turner[6]), or separate genes for each of the associated defects noted, such as dystrophy of the sweat glands, hair, patellæ, etc. It is assumed that the genes come together by chance association as in Mendelian polyhybrids, or are held together by linkage in one chromosome (Aschner[1]).

Against the theory which states that each single component of the group of characters has its own separate cause, MacArthur[2] notes the following objections: "If the genes assort freely, they cannot produce the correlation observed between the elements of the syndrome; if they are linked, as Aschner maintains, they would tend to go together and produce a correlation, high or low, according to the closeness of the linkage, that might last for generations; but this apparently attractive view encounters serious difficulties; (1) when the syndrome first appeared, the several genes controlling it, must all have chanced to mutate at about the same time, and (2) all have happened to lie in the same chromosome, and (3) most of them to affect similar parts (*e. g.*, skin or ectodermal derivatives) whereas genes appear actually to be distributed at random on the chromosome and to mutate singly and at random in the set.

"It is probable that the components of the syndrome which are generally inherited together also originated together. Accordingly, it would seem best to reject for the present the linkage theory, at least in the form presented, as a much less satisfactory explanation of the syndrome than the simpler alternative theory that the whole syndrome arises from a *common* fundamental cause tracing mainly to the differential effects of one gene. In a disease syndrome the associated symptoms commonly arise together, or are traceable to one early starting point, one cause leading to other succeeding effects in train. Analogously, it is an accepted fact that a gene typically exhibits a variety of effects; such diverse effects are probably what are observed in a syndrome."

It has already been shown in the work of MacArthur[7] and

Landauer,[8] that certain syndromes can be plausibly pictured and reasonably explained as arising developmentally, and due to the multiple effects of a gene. "Since gene action is evidently not entirely localized and specific but may reach various, often dissimilar, parts and structures and derivatives even of different germ layers, it may be viewed as operating in a more or less specific way as regards time and rate, producing for instance a retardation of development, acting over a limited period, during which parts capable of responding to its influence are in process of being developed and fixed. The parts most actively developing during the time of action of the gene are most affected; structures once fully developed are not further alterable. Variations of the syndrome would on this view be due either to different residual heredity, to variations in gene potency, as in a multiple allelomorphic series or sometimes even to modifying genes when such entities can be clearly demonstrated."

The social aspect of this problem should not be lightly overlooked. Among 181 cases affected, only 72 have married. G. S. admitted that most of those affected, whom he knew, were quite sensitive with regard to the rather disfiguring nail defects. Although he would not admit that it had any relationship to matrimony, the fact remains that a relatively small number have married, who otherwise seem to be healthy individuals. This is especially unfortunate in females. Those marrying may expect that approximately one-half of their offspring will show some abnormality. On the other hand, normal parents, though belonging to the family tree, may expect normal children. The nature of the disease does not indicate that beneficial results may be expected from glandular therapy. The social facts involved may eventually eradicate this syndrome, and further illustrates nature's tendency to overcome abnormalities in the human race.

Summary. 1. A case of hereditary onychial dysplasia is reported. The findings in the family tree to which this individual belongs are given.

2. A new theory of the genesis of this syndrome is presented. It is suggested that the defects observed are due to the differential effects of one gene (D), acting during the process of development of the three primary body layers, its action ceasing on full development of the various parts. The gene (D) may not be entirely dominant.

3. The social aspects of the syndrome are discussed.

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THERAPY IN CARBOLIC ACID POISONING.

WITH SPECIAL REFERENCE TO THE USE OF OIL ANTIDOTES.

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FOR some years one of the most popular forms of suicide has been by the use of products of the carbolic acid group, and especially with the common commercial preparations such as lysol. A survey of the last 100 cases of poisoning admitted to the New Haven Hospital disclosed that phenol and lysol led the list, comprising the offending agents in 26% of the series; bichlorid of mercury and carbon monoxid constituted 25% and 23%, respectively, of the cases in this group. Phenol and lysol were the cause of death in 45% of those cases with fatal outcome.

The low fatal dosage of this poison and its dramatically rapid and toxic action on the heart, bloodvessels and central nervous system leading speedily through cardiovascular collapse and respiratory failure to death, often within an hour, emphasize the vital importance of prompt and effective treatment.

Among the many antidotes that have been recommended and employed (milk, egg albumin, alcohol, glycerin, sodium sulphate, potassium permanganate, syrup of lime) none has gained universal or enthusiastic acceptance, and only a few have survived in medical practice. Although gastric lavage with alcohol or sodium sulphate is probably the commonest current treatment, it is noteworthy that

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Macht,[14] on the basis of experimental and clinical observations, considered alcohol not only ineffectual, but actually harmful, and Sollmann[21] (p. 644) brands both alcohol and sulphates as "practically useless."

The incessant search for a suitable antidote for carbolic acid poisoning had at one time resulted even in the suggestion that camphor be used, since a mixture of camphor and phenol is comparatively non-irritating locally. But experimental work by Bond and Haag[2] quickly demonstrated that the two drugs have similar central nervous system actions, and that camphor definitely increases the toxicity of peroral phenol.

Robertson's exsanguination-transfusion procedure[18] was also tried in experimental phenol poisoning in dogs by Haskell and co-workers[9] in an attempt to improve the therapeutic attack. They found this procedure to be as valueless for phenol as it proved to be in mercuric chlorid poisoning.[10]

The question of the value of alcohol in the treatment of acute carbolic acid poisoning deserves special attention. The history of how alcohol came to be employed wrongly is given by Macht[14] and Wilbert.[27] Alcohol still enjoys wide use either in dilutions ranging from 10% to 40% or in the form of strong whiskey. There is little unanimity of opinion, however, as to its value. Most of the older textbooks of toxicology recommend its use, and do not even warn against leaving it in the stomach. Sollmann[21] (p. 644), as stated, though branding alcohol as a useless chemical antidote recommends that a 10% solution might be employed as a lavage, to be followed by warm water. Underhill[25] (p. 187) suggests a similar procedure. The theory underlying the use of alcohol seems to be that, since it is an excellent solvent for phenol and can be shown to be effective in the local treatment of phenol skin burns, therefore it must necessarily, when given for peroral carbolic acid poisoning, dissolve the phenol, delay its absorption, and prevent caustic lesions of the gastric wall. It has been shown, however, by Clarke and Brown[4] that local gastric lesions from carbolic acid are as severe when phenol is given in alcohol or glycerin solutions, as when given in watery solutions. These same authors, in addition, found no evidence for a chemical antagonism between alcohol and phenol, and could not convince themselves from both clinical and experimental investigations that alcohol had any superiority over water as a lavage medium. Indeed alcohol and phenol placed in the stomach gave results no different from those with phenol alone. Macht[14] found that gastric lavage with alcohol following experimental phenol poisoning in dogs and cats tended to increase the rapidity of onset and severity of symptoms, and to hasten death. It must be remembered that alcohol is one of the few drugs that is absorbed from the stomach, and during absorption carries the dissolved phenol along with it. Indeed, the gastric irritation and vasodilatation resulting from alcohol may tend to hasten absorption. That this is so might be inferred from the work of Dunn and Perley,[5] who noted that when phenol was administered in alcohol by stomach tube to rabbits the free blood phenol rose more rapidly than when phenol was given alone, although the final levels reached before death in the two groups were essentially the same. These same authors note an apparent increase in toxicity when alcohol is given with phenol and call attention to the possibility of superimposed alcoholic poisoning.

The conclusion to be drawn from the more carefully performed experimental work and critically interpreted clinical data is that alcohol probably does little if any good in phenol poisoning, and may actually do harm.

Notwithstanding the arguments for and against the use of alcohol or any other therapeutic measure, it is evident to anyone who surveys the literature on phenol poisoning, or attempts to treat these unfortunate cases, that a satisfactory antidotal agent is still lacking.

Absorption, Fate and Excretion of Phenol. An understanding of the absorption, fate and excretion of phenol is essential before rational and effective therapy can be instituted. Phenol, C_6H_5OH, carbolic acid, has the characteristic properties of the series of antiseptic benzol derivatives so widely used in industry and medicine. It is slightly soluble in water (1 to 15) but readily miscible in all proportions with alcohol, glycerin and fats. It is not a true acid, and injures tissue by virtue of its being a general protoplasmic poison. It is readily absorbed from all surfaces of the body. The gastro-intestinal absorption, although rapid at first, is slowed after a short interval and may even stop completely, due to local circulatory changes (Sollmann and co-workers[23]). This is an important consideration in the treatment of peroral poisoning, for one may still recover phenol from the stomach for some interval after ingestion. In experienced hands, the use of the wash-out tube is usually indicated, and although discretion is necessary in deciding when to employ it, the danger of perforation of the injured esophageal or gastric wall is probably overemphasized. The phenol after absorption is distributed throughout the tissues of the body. It rapidly leaves the blood, and the higher concentrations are found in the liver, brain and kidneys. From 25% to 67% is completely burned by the body, and conjugation of much of the remainder represents an important protective mechanism of the animal organism. A small part of the carbolic acid is oxidized in the body to hydroquinone and pyrocatechin. That which is not burned is excreted in the urine, a trace being eliminated in the sweat. The urinary phenol is both conjugated, especially as ethereal sulphates and phenolic glycuronates, and unconjugated, the former increasing in amount as the total phenol content of the urine increases. The site of conjugation of phenol in the body has been the subject of considerable investigation. Pelkan and Whipple[15] maintain that the liver is the only organ performing this function, whereas Smith,[19] in a recent work, claims that the kidneys and intestines also participate. The occurrence of phenol-sulphonates in the urine led to the mistaken use of sulphates in the attempt to detoxify carbolic acid in the body. As is occasionally the case with a therapeutic measure whose chief virtue is its novelty, the sulphates were reported to be very useful in treating patients poisoned with phenol. That sulphates are not readily absorbed by the alimentary canal is common knowledge, and even if they were, there is evidence to show that sulphates or inorganic sulphur compounds do not increase conjugation. At any rate, the combination between phenol and sulphates does not occur in the intestinal tract, thus rendering oral sodium sulphate for antidotal purposes a useless gesture. The type of conjugation that does occur in the tissues is very slow, so that even when injected intravenously, sulphates are ineffective (Sollmann and Brown[22]). Indeed, as long ago as 1895, Tauber[24] noted that oral, subcutaneous or intravenous sodium sulphate did not protect against the just fatal dose of subcutaneous phenol in rabbits. It would appear that any slight value the sulphates may occasionally have in the peroral therapy of phenol poisoning is probably due to the purgative effect

of sulphate salts. The symptoms of acute poisoning, in addition to the local effects at the sites of absorption, are mainly referable to the cardiovascular and nervous systems, and the kidneys, all of which are quickly involved. Cardiovascular collapse may ensue from a direct depressant action on the heart muscle and from dilatation of the bloodvessels, with a consequent marked fall in blood-pressure (Gunn[8]). Faintness, weakness, tremors, and respiratory embarrassment and depression are all attributable to the effects of the drug on the central nervous system. In some animals, characteristic and marked generalized clonic convulsions occur, but these are rarely seen in man. The renal damage may result in oliguria and serious impairment of the water and electrolyte balance of the body. The scanty, smoky urine contains albumin, casts, blood (Wakeman and coworkers[26]) and paired phenolic products.

The Rationale of Therapy in Carbolic Acid Poisoning. This understanding of the absorption, fate and excretion of phenol should now make it obvious that the immediate and most important efforts should be made to prevent or delay the absorption of the poison from the alimentary tract. No adequate means are as yet available for dealing with phenol once it has been absorbed, and to hasten its excretion by the kidneys would hardly alter the course of acute poisoning for several reasons. By the time the renal elimination of phenol is well under way, the kidneys are already injured, damage has been done to the more vulnerable cardiovascular and nervous systems, and excretable phenolic products have already been largely detoxified by the organism through conjugation.

How may one prevent or delay absorption of carbolic acid after ingestion? Three ways immediately present themselves: (1) The phenol may be removed by the stomach tube and lavage. (2) A selective solvent may be administered whose affinity for phenol exceeds that of the protoplasm of the enteric wall, and absorption would thus be prevented or delayed. This solvent could also serve as an efficient lavage medium. (3) One may hasten the passage of the phenol, preferably after it has been taken up by the solvent, along the intestinal canal. This latter method would apply mainly to that portion of the phenol which had passed the pylorus or escaped stomach lavage; it could be accomplished by a carefully selected cathartic. The ideal solvent should, of course, hold the phenol inert; should not itself be absorbed by the gastro-intestinal tract; should not be broken down by enzyme action; and should be harmless.

In view of so dire a need for an acceptable antidotal solvent, it is natural that great interest should be aroused by Gibbs'[7] recent proposal. He advises the use of paraffin oil* in phenol poisoning and describes it as a simple, effective, safe and logical agent. The rationale of his treatment seems to be based on the presumption that carbolic acid is more soluble in mineral oil than in water, and

* Synonyms for paraffin oil are: Liquid Petrolatum, U. S. P.; Liquid Paraffin, B. P.; white mineral oil.

theoretically leaves the watery medium of the stomach contents for that of the oil, in which it remains pharmacologically inert. Gibbs' treatment of a poisoned patient would require simply the oral administration of a liberal quantity of paraffin oil, which would theoretically take up the carbolic acid efficiently; and since the oil is entirely non-absorbable, it readily assists its own elimination along with the dissolved poison. It is even suggested that if the above therapy is followed by repeated doses of magnesium sulphate, the use of the wash-out tube may be omitted.

On the basis of Gibbs' claims, paraffin oil would indeed be a splendid antidote, for it is a common and easily available substance, and would fulfill the therapeutic requirements outlined above.

Within a fortnight of the appearance of Gibbs' article, however, this therapeutic measure was attacked by Bowdler,[3] whose comments were published in the same journal. This writer, a former phenol manufacturer, had learned from practical experience and personal observation that phenol was not at all readily soluble in liquid petrolatum in the presence of water, and he questioned the soundness of Gibbs' procedure. This refutation appeared simply as an obscure letter in the section devoted to "Correspondence." Gibbs,[7] in a brief rebuttal, defended his original thesis, but still offered no experimental or clinical evidence for his contentions.

It appears probable that the well known ready solubility of carbolic acid in most fats and oils of vegetable and animal origin gave rise to the mistaken notion, which does not by any means follow, that phenol is also readily and highly soluble in the hydrocarbon series of paraffin oils. To clarify this question we have performed solubility tests.

Experiments on Petrolatum Liquidum. The *in vitro* solubility of both carbolic acid crystals and phenol liquefactum in petrolatum liquidum was tested; various dilutions were prepared at both room and body temperatures. Far from being readily and highly soluble, both of these products were very slowly and poorly soluble in mineral oil. Neither by vigorous and repeated shaking, by elevating the temperature, nor by prolonging the contact for days could the solubility be increased above 1 part in about 50. These results agree with those of Pilcher,[17] but are at variance with the statement of Solis-Cohen,[20] (p. 746) that phenol is "very soluble" in liquid petrolatum. The solubility of phenol in mineral oil in the presence of water was also tested. It was found that when phenol in dilutions of 1 in 5 to 1 in 30 in water were added to paraffin oil, the latter took up much less of the phenol than formerly. Since phenol is three times as soluble in water as in mineral oil, and definitely prefers protein to water, it is difficult to understand why one should expect phenol to be soluble in mineral oil in the presence of the watery medium of the gastric contents. If a conclusion were to be drawn from these *in vitro* solubility experiments, it would be that petrolatum liquidum is not the long-sought antidote for carbolic acid

poisoning, and that its employment might be dangerous in entailing loss of valuable time needed for more effective therapy. It is interesting in this connection to note that Boenninghaus[1] has reported the destruction of the tympanic membrane and corrosion of the external meatus from the use of liquefied phenol in liquid petrolatum as ear drops for earache.

Because of the importance of confirming definitely the conclusions suggested by the above *in vitro* tests, it was thought desirable to submit the question to actual animal experimentation, even though it seemed unlikely that mineral oil might still delay absorption by some other, perhaps mechanical, means. The necessity for such verification was brought home to us more pointedly by the knowledge that the mineral oil therapy of carbolic acid poisoning had permeated into hospital emergency rooms, and had at one time gained a brief trial at the New Haven Hospital. Furthermore, this treatment is recommended in the current edition of a well-recognized textbook of therapeutics (Beckman,[28] p. 696).

Procedure. Normal, adult albino rats, weighing from 100 to 300 gm., and maintained in good health on an adequate diet were used in 150 experiments. In addition, some experiments were done on other laboratory animals in order to make certain that the results obtained with rats were applicable also to other species. Food was first withheld for 36 to 48 hours to insure that the stomach would be quite free from food, water being supplied *ad libitum*. Freshly prepared phenol liquefactum and the various antidotal agents were administered by stomach tube. All animals succumbing in the experiments were autopsied to rule out traumatic death from stomach tube injury, and to recover for study the gastric contents of carbolic acid and antidote.

It was first necessary to establish the minimal lethal dose of phenol for our colony of rats, since the figures given in the literature were found to be excessively high. Hefter[11] (p. 912), for example, gives the lethal dose for the rat, determined by Duplay and Cazin, as 0.66 gm. per kg. It was determined on the basis of 20 rats that 0.3 gm. of phenol liquefactum* per kg. of rat could be relied on to prove fatal in 85% of the cases, and we have employed this as the minimal lethal dose (M.L.D.). When this dose was reduced to 0.2 gm. per kg., the fatality was less than 50%.

The sequence of development of symptoms after phenol is given to the rat is constant and rapid. For from ½ to 4 minutes (average of 2) the animal presents no signs. Then respiratory distress appears as the first evidence of intoxication, followed quickly by intermittent muscular twitches of the trunk and extremities. Within another minute or two, the rat loses the ability to maintain normal posture. The animal falls on its side and exhibits severe and extremely rapid clonic convulsions resembling running movements. Since phenol in these doses is an efficient local anes-

* One cubic centimeter of phenol liquefactum weighs approximately 1 gm. Phenol liquefactum is about 90% carbolic acid by weight.

thetic, the animals give no evidence of pain. The convulsions persist until death approaches, becoming less violent toward the end, due probably to the intervention of exhaustion and asphyxia. Respiratory failure ends the picture. Death occurs in from 2 to 50 minutes after phenol (average of 27) but is occasionally delayed for several hours. If recovery is to occur, an early sign is the ability of the rat to regain its feet. Recovery, as far as the appearance and activity of the animal are concerned, is complete, and no late deaths have been noted.

Due to the rapidity of onset of severe symptoms, the antidote had to be given almost directly after the phenol. If one waited for more than 2 or 3 minutes, *i. e.*, until the animal exhibited marked central nervous system signs, then the passage of the stomach tube to administer the antidote was in itself likely to precipitate or hasten death, due to the unavoidable slight respiratory embarrassment occasioned by this procedure. Consequently, it seemed desirable in testing the value of so questionable a therapeutic agent as paraffin oil to administer the oil even before the phenol. If this alleged antidote should fail to protect against the poison under these especially favorable circumstances, then it would indeed be useless to employ it clinically.

TABLE 1.—INEFFECTIVENESS OF MINERAL OIL AS AN ANTIDOTE IN PHENOL POISONING IN RATS.

No. of rats.	Dose of phenol, M.L.D. = 0.3 gm. per kg.	Oil antidote.	Time of administration of antidote, before or after phenol.	Volume ratio of $\frac{\text{antidote}}{\text{phenol}}$	Intensity of symptoms.	Average time after phenol administration.			Survivors.	
						Appearance of symptoms.	Death.	Recovery.	Number.	Percentage.
						min.	min.	hrs. min.		
20	M.L.D.	None	...	..	Severe	2.0	27	3 ..	3	15
20	M.L.D.	Mineral	Before	40	Severe	1.3	33	3 20	4	20
5	2 M.L.D.	Mineral	Before	40	Severe	0.5	12	.. ..	0	0

Mineral oil was administered to rats by stomach tube in a volume equal to forty times that of the phenol liquefactum given. This volume ratio of oil to phenol closely approximated the solubility ratio without unduly encroaching on the limit of capacity of the rat's stomach. The animals were observed for at least 5 minutes to make certain that nothing in connection with the giving of the oil had affected them adversely; and phenol liquefactum was then given. Twenty rats were given the M.L.D. of phenol following mineral oil, and 5 rats were given twice the M.L.D. Of the former group, 4 lived, 20% survival. Of the latter group, all succumbed. These results are given in Table 1. It is readily seen that mineral

oil, even when given *prior* to phenol does not protect against the poison. The percentage survival was raised from 15%, when no antidote at all was given, only to 20%, a negligible difference. The giving of mineral oil prior to phenol did not delay the onset of symptoms of poisoning or mitigate their severity. Indeed, if it did anything, it increased slightly the speed with which symptoms developed (average of 1.3 minutes after phenol as compared with 2 minutes for the controls). Nor did the paraffin oil manifest any appreciable tendency to delay the time of death, the rats dying in an average of 33 minutes after phenol as compared with 27 minutes for the controls. Likewise, the time needed for recovery was not shortened. An animal was regarded as having recovered when it had regained its feet and ceased to manifest tremors. An examination of the stomachs after death revealed the unabsorbed, undissolved phenol clearly layered underneath the much larger bulk of supernatant liquid petrolatum. Qualitative tests of the oil showed that only a slight trace of carbolic acid had been dissolved.

Since in these experiments only the minimal fatal dose of carbolic acid had been used, and the paraffin oil had been given *beforehand*, one is justified in concluding that not only is mineral oil an ineffectual antidote, but that it fails even to exercise a mechanical hindrance to the rapid absorption of phenol.

In addition to the aforementioned experiments on rats, we tested the antidotal value of liquid petrolatum in 2 each of rabbits, cats, dogs and guinea pigs. In no instance did it protect in the slightest against the fatal dose of carbolic acid. Although these experiments on other species were limited, we believe the general conclusions from the more extensive rat experiments are applicable to other animals, because the principles underlying the absorption, fate and excretion of phenol are essentially similar, and the factors pertaining to absorption in particular are largely mechanical (time, amount, dilution, solubility, absorbing surface, etc.). In this connection it may be mentioned that Sollmann and co-workers[23] found the absorption of phenol to be quantitatively identical in dogs and cats, despite the greater susceptibility of the cat for phenol; and absorption from the stomach and intestines is similarly identical.

Experiments With Olive Oil. Because of these disappointing although predictable and anticipated results with paraffin oil, it was decided to seek a commonly available oil which *would* accomplish what had mistakenly been claimed for liquid petrolatum. The knowledge that phenol is readily miscible with true oils naturally confined the search to those oils of animal and vegetable origin. When none was found that met our requisites we consulted Dr. Wm. E. Anderson of the Department of Physiological Chemistry, who stated that he knew of no true fat that was not readily absorbed by the gastro-intestinal tract. It seems, indeed, from the studies of Langworthy[13] on 21 animal and 33 vegetable fats, and 3 hydro-

genated oils that their digestibility is uniformly almost complete (approximately 81% to 99%). A mixture of tripalmitin and tristearin (Holt and co-workers[12]) was the only fat that was found with a relatively low digestibility (61.5%). This mixture, however, is not only difficult to obtain, but has a melting point of 50° C., both factors precluding its usefulness. It thus became evident that any common true oil which would act as a solvent for carbolic acid would also in time be digested and absorbed. Recognizing the importance of delaying absorption, and realizing the possibility of using the solvent chiefly as a lavage medium, we decided to use olive oil in the place of mineral oil in experiments similar to those described above. Since phenol death is usually rapid, it was felt that any agent which prevented a lethal concentration of phenol from accumulating in the tissues would allow one to play for just the necessary amount of time that might spell the difference between life and death, in the interim, of course, employing means to remove the unabsorbed poison or hasten its passage from the body.

Olive oil, which has the advantages of being a common, cheap, bland, and not unpleasant household commodity, is a ready solvent for carbolic acid crystals or phenol liquefactum. We tested the *in vitro* solubility of both of these substances in olive oil at room and body temperatures. Phenol liquefactum was very quickly soluble in olive oil at room temperature, in a ratio of 0.9 to 1, and even more soluble at 37° C. Phenol in crystallin form was more slowly soluble and required some shaking, but at body temperature it was almost as soluble as the liquefied form.

Eleven rats were given olive oil, in a volume 40 times that of the M.L.D. of phenol liquefactum, 5 minutes prior to the poison. Ten animals lived, 91% survival, as compared with 20% for the comparable liquid petrolatum group. We then gave twice the M.L.D. in 15 rats but administered olive oil in a volume only 20 times that of the phenol. In this series, 8 animals survived (53%) despite the larger dose of poison and the marked relative reduction in the amount of antidote. In another 10 rats, the M.L.D. of carbolic acid was given first, and then followed in from ½ to 3 minutes by olive oil in a volume 40 times that of the phenol. Of these, only 3 animals survived, a percentage of 30. The results of these experiments with olive oil compared with those of mineral oil appear in Table 2.

These results suggested that there was a direct quantitative relationship between, on the one hand, the amount of poison and its degree and speed of absorption, and, on the other hand, the volume of antidotal solvent and the rapidity and affinity with which it took up the poison. That the time element was of paramount importance was indicated by the fact that when olive oil was given immediately prior to the M.L.D. of phenol, 91% survived; but when it was given immediately after, only 30% survived. It should be

reëmphasized that the rat appears peculiarly susceptible to carbolic acid especially in the speed with which violent symptoms (mainly nervous) and death ensue, and therefore an agent which delayed or averted symptoms or death in the rat when double the M.L.D. was given must have some merit. Macht,[14] in commenting on the use of twice the minimal lethal dose of phenol in his experiments, calls this an "enormous dose." It was also noteworthy that olive oil often delayed death, when it occurred, for several hours; and it not only delayed the onset of symptoms, but in nearly every instance greatly reduced their severity. Whereas the animals not given olive oil developed neuromuscular and respiratory signs in 2 minutes on an average, those given olive oil prior to phenol did not show signs for 9 minutes after phenol was given. Death, when it occurred, was greatly delayed, and the time needed for recovery markedly shortened. Even in the group with only 30% survival, death did not occur for 3 hours. An examination of the contents of the stomach showed a much more complete mixture of the phenol and olive oil than was the case with mineral oil.

TABLE 2.—SUPERIORITY OF OLIVE OIL OVER MINERAL OIL AS AN ANTIDOTE IN PHENOL POISONING IN RATS.

No. of rats.	Dose of phenol, M.L.D. = 0.3 gm. per kg.	Oil antidote.	Time of administration of antidote, before or after phenol.	Volume ratio of $\frac{\text{antidote}}{\text{phenol}}$.	Intensity of symptoms: mod. = moderate.	Average time after phenol administration.			Survivors.	
						Appearance of symptoms.	Death.	Recovery.	Number.	Percentage.
						min.	hrs. min.	hrs. min.		
20	M.L.D.	Mineral	Before	40	Severe	1.3	.. 33	3 20	4	20
11	M.L.D.	Olive	Before	40	Mild*	9.0	5 ..	2 ..	10	91
5	2 M.L.D.	Mineral	Before	40	Severe	0.5	.. 12	.. ..	0	0
15	2 M.L.D.	Olive	Before	20	Mod. to severe	4.0	1 40	2 20	8	53
10	M.L.D.	Olive	After	40	Mod. to severe	†	3 ..	5 ..	3	30

* One rat had no symptoms.
† Olive oil was given, as a rule, after symptoms appeared.

These encouraging results immediately suggested that the percentage of survivals might be increased by hastening the elimination of the olive oil-phenol solution. Castor oil was selected as the cathartic of choice, since it is an oil in which *in vitro* tests showed phenol liquefactum to be even more soluble than in olive oil, and

a hydrogogic purgative is naturally to be avoided. Castor oil, furthermore, is often used for the emergency treatment of carbolic acid skin burns in establishments manufacturing this chemical. In order to obviate an additional passage of the stomach tube, the castor oil was mixed with the olive oil in the proportion of 1 part of the former to 4 parts of the latter. Twelve rats were given this mixture of oils 5 minutes prior to, and in a volume 20 times that of, 2 M.L.D. of phenol. Nine rats survived, 75%. Despite this very large dose of poison, two rats were completely protected from symptoms. The time for recovery was shortened, and death was delayed. Symptoms were milder, and their onset was delayed. These results are presented in Table 3, which compares them with those obtained on rats receiving olive oil. One sees that the percentage survival is raised to over 40% by adding castor oil to the olive oil, thus aiding the elimination of the oil-phenol solution, and preventing the digestion and absorption of the antidote. Since phenol is freely miscible with castor oil, it might occur to one to use this oil alone; but a few preliminary experiments revealed, as anticipated, an appreciable fall in the percentage of survivals as compared with the olive oil-castor oil combination. It is probable that the inflammatory reaction incited by such necessarily large doses of castor oil served both to promote shock and to facilitate absorption of the poison by local vasodilatation. Death, however, when pure castor oil was given after phenol, was delayed many hours, and the symptoms were mild and late in appearing.

TABLE 3.—CASTOR AND OLIVE OIL MIXTURE AS AN ANTIDOTE IN PHENOL POISONING IN RATS.

No. of rats.	Dose of phenol, M.L.D. = 0.3 gm. per kg.	Oil antidote.	Time of administration of antidote, before or after phenol.	Volume ratio of antidote : phenol	Intensity of symptoms: mod. = moderate.	Average time after phenol administration.				Survivors.	
						Appearance of symptoms.	Death.		Recovery.	Number.	Percentage.
						min.	hrs.	min.	hrs. min.		
15	2 M.L.D.	Olive	Before	20	Mod. to severe	4.0	1	40	2 20	8	53
12	2 M.L.D.	Olive and castor	Before	20	Mild to mod.*	6.0*	2	50	1 55	9	75

* Two rats showed no symptoms.

The next logical step was to use olive oil simply as a lavage medium. In 10 rats, therefore, the M.L.D. of phenol liquefactum was given, followed in ½ to 2 minutes by 40 times the volume of

olive oil, and the stomach pumped out immediately. All 10 rats lived, 100% survival. In 10 other rats, 2 M.L.D. were given and followed by only 20 volumes of olive oil, the latter then being pumped back. Eight of these rats lived, 80% survival. The pumping was done within 30 seconds, as a rule, after the olive oil was given, because a longer wait necessitated a second passage of the stomach tube, and this was almost certain to coincide with or precipitate the onset of severe symptoms, and aggravate the latter through respiratory embarrassment. In spite of the short interval of time allowed for the olive oil to dissolve the phenol, sufficient of the latter was removed to give the results recorded in Table 4, which contrasts these with comparable experiments in which pumping was not attempted. These figures again illustrate the importance of removal of the poison-antidote combination, in this instance by pumping the stomach. Examination of the stomach contents again showed considerable phenol taken up by the oil. Here, also, when death occurred, it was delayed, often for 2 or 3 hours. Symptoms were milder, even though their onset preceded the administration of the antidote.

TABLE 4.—EFFECTIVENESS OF OLIVE OIL LAVAGE IN PHENOL POISONING IN RATS.

No. of rats.	Dose of phenol, M.L.D. = 0.3 gm. per kg.	Oil antidote.	Time of administration of antidote, before or after phenol.	Volume ratio of $\frac{\text{antidote}}{\text{phenol}}$	Gastric lavage.	Intensity of symptoms: mod. = moderate.	Average time after phenol administration.		Survivors.	
							Death.	Recovery.	Number.	Percentage.
							hrs. min.	hrs. min.		
10 . .	M.L.D.	Olive	After	40	No	Mod. to severe	3 ..	5 ..	3	30
10 . .	M.L.D.	Olive	After	40	Yes	Mild to mod.	.. ..	2 ..	10	100
10 . .	2 M.L.D.	Olive	After	20	Yes	Mod. to severe	2 30	4 ..	8	80

In an attempt to follow through the inferences of these results and to simulate the clinical treatment of phenol poisoning, another group of 10 rats was given 2 M.L.D. of the acid, followed by olive oil and stomach lavage; but in these rats an additional dose of olive oil was given after the pumping. Although this is logical therapy, namely, to allow some fresh antidotal solvent to remain in the stomach after lavage to take care of the poison not withdrawn or that which has passed beyond the pylorus, the percentage survival was not raised above the 80% obtained in experiments with com-

parable dosage and procedure except for omitting the final instillation of olive oil. We believe that this is due to the excessive asphyxia resulting from the additional time needed for changing syringes and injecting the last dose of olive oil. By the time this step is reached in the treatment, severe nervous symptoms are rapidly developing and the respiratory embarrassment at this critical time offsets any advantage of this procedure in the rat.

Discussion. From these experiments there is little doubt that mineral oil has no place in the physician's limited armamentarium against acute carbolic acid poisoning. Phenol and related substances are very commonly used chemicals, and still cause a large proportion of poisoning deaths. The treatment at present is admittedly so limited and ineffectual that when a new therapy is published, often with uncritical and exuberant claims, it is likely to gain widespread and unwarranted use. Years sometimes pass before the disappointing results cause it to be discarded. For this reason it was considered desirable to submit the question of the antidotal value of mineral oil to animal experimentation, and to raise a note of warning concerning its use in human poisoning cases. The experiments with olive oil grew out of the failure of petrolatum liquidum to achieve the results which might reasonably be expected of rational treatment. The survival figures for olive oil cited above seem definitely encouraging. We have had no opportunity as yet to apply the implications of this work to human cases, and, therefore, can offer no direct evidence on this point. While we realize all the caution and qualifications necessary for the transference of the conclusions drawn from animal investigation to man, we still feel that since the treatment of phenol poisoning is so limited and unsatisfactory, the trial of olive oil is justifiable. As emphasized previously, in carbolic acid poisoning, "anything which helps a little may help a lot." Olive oil could be administered promptly in as large a quantity as possible, preferably by having the patient drink it if he is able. Then, in skilled hands, the stomach tube can usually be quickly passed with safety and lavage performed with generous quantities of olive oil. Before removing the stomach tube fresh oil could be instilled and allowed to remain.

It is not our purpose to undertake here a complete discussion of the management of the phenol-poisoned patient, but only to emphasize the importance and nature of the immediate emergency therapy. Symptomatic and supportive measures are employed as the particular needs of the case dictate. The physiologic principles of treatment outlined recently by Peters and co-workers[16] for acute mercury poisoning apply equally well to the carbolic acid case, since there is analogous gastro-intestinal, renal and vascular injury with consequent diminution of serum proteins, and disturbance of the fluid and salt stores of the body. Particular attention should be paid to the administration of liberal parenteral fluids and electrolytes of

suitable composition and, perhaps, to the provision of blood by transfusion. Details of this management may best be gleaned directly from the reference cited.

We are not prepared to suggest the use of a cathartic because of the salt and water disturbances it may possibly entail and the additional gastro-intestinal injury; but if one is given, the choice should fall perhaps on castor oil, which in itself is an even better solvent for carbolic acid than is olive oil. Poisoning by lysol and other cresol derivatives has, in general, the same therapeutic implications as those described for phenol.

Summary. 1. *In vitro* and *in vivo* experiments with petrolatum liquidum did not substantiate the claims made for it as a therapeutic antidotal agent in the treatment of acute carbolic acid poisoning.

2. Similar experiments with olive oil gave promising results.

3. The principles underlying the emergency treatment of phenol poisoning were outlined, and the possible use of olive oil in human cases discussed.

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(Titles have been omitted for sake of brevity.)

THE RECOGNITION OF SOME FORMS OF INTRACRANIAL LESIONS.*

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The ultimate object of a Roentgen ray examination is not merely to determine the presence of lesions but also to diagnose the nature of the pathologic process. It is, of course, impossible to attain this objective in more than a small percentage of the total number of cases examined, but it is not infrequently possible, in cases suffering from intracranial disease, to be able to state the location of a lesion, which is of tremendous importance even though its nature may remain obscure. It is difficult to state accurately what percentage of cases suffering from intracranial disorders will give sufficient evidence in the Roentgen ray film to permit the recognition of a lesion, or how early such evidence will become visible, because it is comparatively rare for a patient to present himself for examination before the symptomatology becomes rather well established. Unfortunately, both the patient and his physician are reluctant to admit the possibility of intracranial trouble before the condition has progressed to such an extent that there remains but little doubt. Of the proved cases of intracranial disease that we see, which usually present strongly suggestive symptoms, about 70% will give evidence in the films to indicate the presence of disease, while in about 30% it will be possible to arrive at a fairly accurate localization of the process, and not infrequently state the nature of the lesion.

The general signs of intracranial disease are those of pressure, such as: atrophy of the sella turcica, increase in number and depth of the convolutional impressions together with a lack of clarity of their outlines, separation of the sutures, and general halisteresis of the skull bones. The localizing signs are 5 in number: calcification, bone proliferation, bone absorption, localized areas of hypervascularity, and last but not least, displacement of the pineal shadow. In the presence of any one of the localizing signs, a diagnosis may be possible, and with more than one present the lesion can usually be localized and often identified. It is of considerable importance, before beginning a study of roentgenograms of the skull, to be in possession of a history of the case, and if possible, the clinical findings. It might also be added that it is futile to attempt to pass opinions on films of the skull which are not of excellent technical quality and stereoscopic.

The first group of lesions to be considered is that composed of

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the so-called bloodvessel tumors, which constitute only about 2% of all intracranial tumors. These are usually divided into the vascular malformations and true tumors. The malformations may be again divided into the venous angiomas and the arteriovenous or aneurysmal angiomas. These malformations are not true tumors, for as pointed out by Cushing and Bailey, glial tissue can be demonstrated between the vessels comprising the lesion, and as they are essentially congenital in type, they are most frequently discovered in young people. The venous malformations may be found in several forms, but for our purpose they can be grouped under the one heading of angioma venosum. These lesions usually are deeply seated in the posterior half of the cerebrum, although they may begin on the surface of the cortex. The symptomatology is usually slight. Perhaps the most common symptom is Jacksonian attacks. At other times they may be discovered quite accidentally. In about 50% of these lesions, sufficient calcification will be present in the walls of the vessels to make them visible in the roentgenogram, and their recognition depends upon the appearance of this calcification, which is usually in parallel lines which often take on a convoluted form. With a venous lesion there is usually no increase in the depth of the vascular channels on the inner table of the skull and there is no evidence of increased intracranial pressure. In Figures 1 and 2 we have an example of such a lesion which was accidentally discovered in an examination of the sinuses. This case emphasizes the advisability of not confining such an examination to small blocked out areas of the sinuses themselves.

The arteriovenous angiomas also show calcification in about 50% of the cases, and like the angioma venosum they are found almost exclusively in the cerebrum, but unlike the venous angioma they are usually accompanied by a marked increase in the size of one or more vascular channels, and not infrequently give rise to some increase of intracranial pressure. These bloodvessel anomalies may, as previously stated, originate on the cortex and burrow deeply in a somewhat conical shape to finally produce a hemorrhage into the ventricular system. Figure 3 is a good example of an arteriovenous angioma in which can easily be seen the large vessel channels and also, upon close examination, parallel streaks of calcification can be recognized. It might not be amiss to mention the fact that in the presence of an arteriovenous angioma not infrequently a bruit may be heard on careful auscultation of the skull—a procedure all too often neglected. It is of considerable importance to be able to recognize these bloodvessel malformations because their treatment is not surgical, as a rule, for the reason that the surgical removal of such a vascular anomaly usually presents such a formidable problem that its solution is often impossible. Hence, radiotherapy is probably the treatment of choice at present.

Let us now consider the true bloodvessel tumors which are the hemangioblastomas. These occur almost exclusively in the posterior fossa in children, and their site of election is in the posterior portion of the fourth ventricle, so that as may readily be seen, they are usually accompanied by a rapid rise of intracranial pressure and therefore, untreated, their history is short. They are usually composed of true angioblasts and may become cystic. It is rare to find one of these cysts containing sufficient calcium to cast a shadow in the roentgenogram. When seen at operation, they may easily be mistaken for an angiomatous type of meningioma, although it is comparatively uncommon to find a meningioma in a young individual. Occasionally, these hemangioblastomas may be rather widely spread and appear along the spinal cord and in the retina, and when accompanied by cystic kidneys and cysts of other abdominal viscera the condition is known as Lindau's disease. Occasionally when these cysts occur in the retina they may become calcified and so become visible in the roentgenogram (Fig. 4).

Another type of bloodvessel tumor which can often be identified in the Roentgen ray films of the skull is the cavernous hemangioma. It may occur anywhere in the bones of the skull, but when seen in the vault is usually quite characteristic. It forms a fusiform swelling with, as a rule, bone spiculations appearing at right angles to the tables of the skull. It is markedly hypervascular and gives the bone a honeycombed appearance. The lesion is, as a rule, quite definitely circumscribed and appears characteristically as seen in Figure 5. Occasionally it will not be as clearly defined and will merely produce an area of bone which appears to contain many small pinholes, and must therefore be differentiated from the often noted osteoporosis and increased visibility of the diploë, which is most commonly seen in the superior parietal and frontal regions.

While considering bloodvessel tumors we may speak briefly of aneurysms, which in the skull are not of syphilitic origin. It is quite possible that some may be of arteriosclerotic origin, but it also seems highly probable that many of them are the result of congenital abnormalities of the vessels and their walls. The most common arteries to be involved are those about the circle of Willis and the basilar artery. When an aneurysm occurs on either side of the sella it usually produces unilateral erosion of the bones forming the sella turcica and often calcium will be deposited in the vessel walls so that curvilinear streaks of increased density may be seen arching above the pituitary fossa, and in addition it is not uncommon to find erosion of the homolateral optic foramen. Figure 6 is a good example of a carotid aneurysm. Aneurysms of the basilar artery are not easy to recognize as they rarely calcify, so that their recognition is usually dependent upon clinical findings or possibly encephalography.

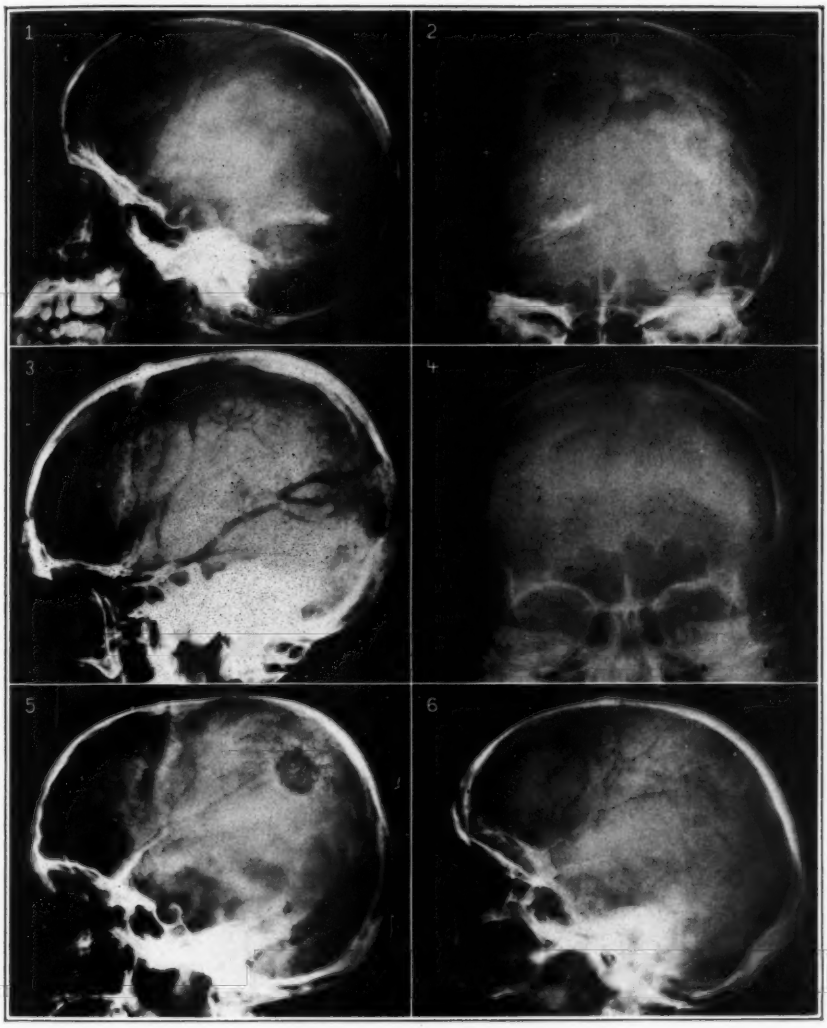

FIG. 1.—A case of angioma venosum. Note the calcification above the tentorium in parieto-occipital region, without signs of increased pressure or hypervascularity.

FIG. 2.—Same case. Note linear parallel streaks of calcification extending obliquely toward midline.

FIG. 3.—Arteriovenous angioma characterized by enlarged vessel channels which are chiefly arterial, and small flecks of calcification in vicinity of the angular gyrus.

FIG. 4.—A case of Lindau's disease. Note circular shadows of calcification in each orbit.

FIG. 5.—Typical case of hemangioma of bone. Occasionally a small anomalous Pacchionian granulation might simulate such a lesion.

FIG. 6.—Aneurysm of internal carotid artery. Note typical curvilinear streaks of calcification and marked destruction of sella turcica.

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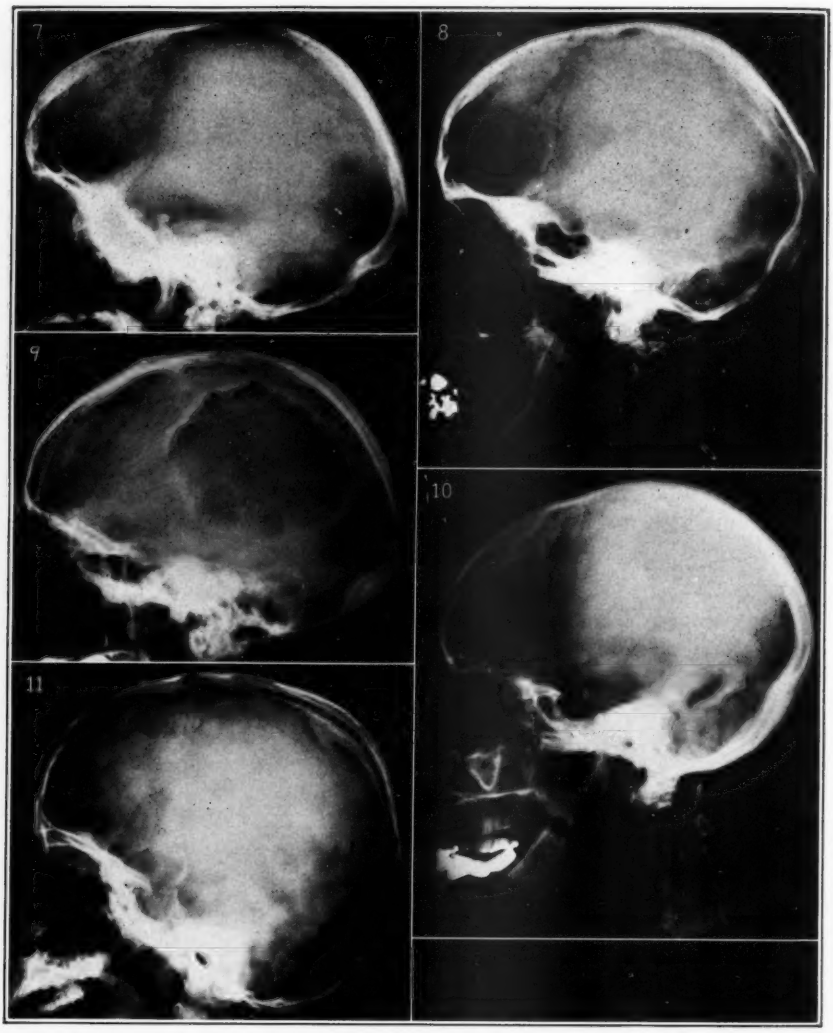

FIG. 7.—Bony overgrowth due to a meningioma of the lesser wing of the sphenoid bone. The extent of the bony change is not a measure of the extent of the tumor.

FIG. 8.—Meningioma producing bony hypertrophy of inner part of sphenoid ridge and extending into the olfactory groove.

FIG. 9.—The large defect in the parietal bone is produced by an epidermoid cyst chiefly involving the diploë. Note the irregular borders of the defect.

FIG. 10.—A typical ballooned sella turcica produced by a chromophobe pituitary adenoma. Note lack of signs of generalized pressure or changes suggesting acromegaly.

FIG. 11.—A good example of a craniopharyngioma. Note the calcification above and the destruction of the sella turcica, together with general signs of elevated intracranial pressure.

The meningiomas, or meningeal fibroblastomas, constitute a group of tumors which are not malignant and do not invade the brain. Their growth is slow and the clinical symptoms may be comparatively slight. These tumors account for about 13% of intracranial new growths and because they are not invasive their complete removal is often possible. It is, therefore, of considerable importance to be able to recognize the presence of a meningioma before it attains such a size that its removal becomes impossible. They probably originate in the meninges and are usually found in certain portions of the skull which constitute their sites of election. About 35% occur over the convexities anterior to the fissure of Rolando. About 25% will be found in the so-called parasagittal location which is along the course of the longitudinal sinus or in the falx. About 12% will be found in the vicinity of the sphenoid ridges and from this location they may extend into the orbits. A slightly smaller percentage will be found involving the petrous ridges. A small percentage will be found originating in the vicinity of the tuberculum sellæ, whereas about 9% occur subtentorially. As a rule, these tumors do not produce much if any increase of intracranial pressure, with the exception of those occurring subtentorially, so that it is not common to find any marked destruction of the sella turcica or other signs of increased pressure. The most characteristic change which can be recognized in the roentgenogram is bone production which is a common finding in the presence of a meningioma. This bone production is apt to be sclerotic when it involves bone of cartilaginous origin, and more spiculated when involving the bones of the vault. It is not uncommon to find sufficient calcium in a meningioma to cast a shadow in the roentgenogram. This shadow is usually homogenous and not dense. If such evidence of calcification is seen in the presence of bone hypertrophy it is almost certainly in one of these tumors. Some of the changes which we have come to recognize as characteristic are shown in Figures 7 and 8. In brief, then, if bony overgrowth is seen in any of the sites of election of the meningiomas, and especially if there is evidence of hypervascularity, there need be no hesitation in making a diagnosis.

Another type of tumor which usually leaves a rather characteristic trade mark is the epidermoid, sometimes known as the cholesteotoma or pearly tumor. This, as the name implies, is of epidermal origin and is most often found in connection with chronic middle ear infections. These tumors may appear in the mastoid antrum but may also be found almost anywhere in the brain or skull. When they occur in the bones of the vault, they usually appear in the diploë and produce an irregular area of osteolysis which is often surrounded by bone of slightly increased density. The margins of the defect are, as a rule, somewhat serpentine in shape and as the tumors are avascular there is no increase in surrounding vascularity.

It is only when the epidermoids involve the bones of the vault or mastoid region that they can be readily recognized in the roentgenogram. The characteristic change produced by such a tumor is well seen in Figure 9. It might be mentioned that such a lesion could be simulated by a leptomeningeal cyst so that such a possibility must be borne in mind when making a differential diagnosis.

Another group of tumors comparatively easy to recognize in the roentgenogram is the pituitary adenoma; but it does not suffice to be able to state merely that a pituitary tumor is present, for in addition we should state whenever possible the type of adenoma we are dealing with. This often can be done if we bear in mind that the chromophobe type of tumor is the most common. It produces the greatest amount of destruction of the sella turcica, and practically no other bony change. The chromophil type of tumor causes less sella destruction but produces the typical changes of acromegaly, or in young people, gigantism. The basophilic adenoma usually produces no change in outline of the sella turcica, because the tumors are often microscopic in size; but there will be a generalized halisteresis which gives a somewhat granular appearance to the vault, simulating slightly the changes commonly associated with hyperparathyroidism. It is also to be noted that as a rule the pituitary adenomas do not give rise to any elevation of intracranial pressure. It also must be borne in mind that sella changes very similar to those produced by pituitary tumors can also occur in the presence of gliomas, but usually the diagnosis can be made if one is in possession of the clinical findings. Not infrequently a tumor will be met containing both chromophobe and chromophil cells; that is, a mixed type, but usually with one or other type of cell predominating. If one should encounter a large, rather well destroyed sella turcica along with changes suggesting acromegaly, the tumor in all probability would be of the mixed type with the chromophilic cells predominating. Figure 10 is of an intrasellar chromophobe adenoma.

After a diagnosis of pituitary adenoma has been made, and unless the eyesight is immediately threatened, I would strongly recommend radiotherapy as the treatment of choice. In our hands it has proved to be startlingly efficient. We have now had the opportunity of following several cases over a period of years and their recovery is evidently permanent.

There is another tumor which occurs in the immediate vicinity of the sella turcica which can often be recognized. This originates from the remains of Rathke's craniopharyngeal pouch. These tumors are essentially congenital and therefore usually a lesion of childhood. Occasionally, however, one will remain dormant and not become evident until adult life. They are slow growing, usually cystic, and prone to calcify. They tend to grow upward and frequently involve the third ventricle so that an increase of intra-

cranial pressure is a common finding. There may or may not be much sella destruction. These tumors frequently are associated with Froehlich's syndrome and are almost always accompanied by visual disturbances. Calcification above the sella turcica with evidences of increased intracranial pressure usually indicates the presence of a craniopharyngioma. The changes produced by such a lesion are shown in Figure 11.

I have purposely omitted mentioning the gliomas because they constitute an extensive subject in themselves, and there is not sufficient time to discuss them in detail. It might be mentioned that it is frequently possible to state that a glioma is present from the changes seen in the roentgenogram, and as about 13% of them calcify, these can, of course, be definitely localized. Occasionally, it is even possible to actually name the type of glioma present.

In this short presentation I trust I have been able to paint for you a "mental picture" of some of the intracranial lesions that can be recognized in the roentgenograms of the skull.

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THE CEREBROSPINAL FLUID DURING AND BETWEEN ATTACKS OF MIGRAINE HEADACHES.*

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Many of the fundamental factors concerning migraine have never been sufficiently studied. Among these is the relationship of the cerebrospinal fluid pressure and composition to the occurrence of migraine headaches. Riley,[1] in a recent review of the subject of migraine, has emphasized the fact that the data in the literature is based upon the incomplete analysis of fluids from a few cases. There are no reports of the complete findings in an adequate series of cases. For this reason, it is advisable to publish the results of observations of the pressure and composition of the cerebrospinal fluid from 44 patients suffering with migraine. Fifteen of these patients were punctured during an attack.

Bassoe[2] reviewed some of the spinal fluid observations in the literature and quotes Quincke[3] as having obtained pressure readings ranging from 155 to 210 mm. of water during attacks in 3 cases with relief following the lumbar puncture. As reported in the original, 1 of these cases does not appear to be migraine. Kerppola[4] performed a lumbar puncture in 5 cases of "migraine" and found pressures of 80, 110, 120, 190 and 220 mm. of water respectively. Sicard[5] and Sicard and Cambessédès[6] report the findings in a few cases and emphasize the fact that the occurrence of abnormalities in the cerebrospinal fluid is indicative of an organic lesion and is against the diagnosis of "migraine."

Mingazzini[7] described some of the cerebrospinal fluid characteristics in 48 cases of "essential headache." He avoided using the term migraine and indeed many of his cases could not be classified as such. These "essential headaches" he grouped in two types with separate etiologic factors in each group. One, he feels, is due to cerebral arterial spasm; the other, to a temporary hyperactivity of an angioneurotic choroid plexus. In some cases, especially in the latter type, he felt that the spinal fluid pressure was "augmented" but gives no manometric readings as the pressure was estimated from the rate of flow of fluid from the lumbar needle. Only about

* This study was aided by a grant from the Josiah Macy, Jr., Foundation.

50% of his cases showed an "augmented" pressure and it was in these cases that the greatest percentage of relief was obtained by withdrawal of lumbar spinal fluid. Other spinal fluid observations he considered to be normal.

Critchley[8] and Critchley and Ferguson[9] found a normal fluid under a low pressure in cases punctured during an attack of migraine. The actual pressure readings were: 60, 90, 50 and 75 mm. of water (patient in the lateral recumbent position).

One of us with Pool and Lennox[10] in a study of the effect of ergotamin tartrate upon migrainous and non-migrainous patients reported among other observations the cerebrospinal fluid pressure of 10 migraine patients before and after the administration of ergotamin tartrate. It was pointed out that the cerebrospinal fluid pressure appeared to bear no direct relationship to the occurrence or intensity of the headache in these cases. More complete observations of the cerebrospinal fluid from these cases are included in the present study.

Materials and Methods Used in This Study. All of the observations on patients during headache and most of those in the asymptomatic intervals were made by a member of the Neurological Unit. The remaining cases were collected from the records of the other Services of the Boston City Hospital. The chemical determinations on all the fluids were done by the laboratory of the Neurological Unit.

The patients on whom these observations were made were all subject to recurrent paroxysms of headache for a number of years. In all cases, the headache was associated with nausea and in most cases, with vomiting. Many occurred at the menstrual period. Visual disorders, such as scotomata or blurring of vision, accompanied attacks in many of the cases. Vertigo was a frequent concomitant. A hereditary predisposition was apparent in many but no definite etiology could be ascertained in any of these cases. Cases of obvious neuroses were excluded as well as cases of unproven but suspected intracranial pathology.

Lumbar punctures were performed at the fourth lumbar vertebra while the patient lay in the lateral recumbent position with the craniovertebral axis horizontal. Measurements of pressure were made with an open-end (2 mm. bore) spinal fluid manometer attached directly to the needle. A few minutes elapsed before the pressure was recorded in order that the patient might become quiet and relaxed. After all observations of pressure were made, a sample of the fluid was collected for analysis. Cell counts were made in the ordinary blood-counting chamber, the fluids being lightly stained with Unna's polychrome methylene blue. The total protein was determined by the Ayer, Dailey, and Fremont-Smith modification of the Denis-Ayer method,[11] the sugar by the Folin-Wu method as modified by Rothberg and Evans[12] and the chlorids by the Wilson and Ball[13] modification of the Van Slyke method. The colloidal gold reaction was performed by the Lange method as described by Cockrill.[14]

Observations. Our results are presented in Tables 1 and 2. Fifteen observations were made on 15 patients during a typical migraine attack (Table 1). The maximum spinal fluid pressure was 190, the minimum 40, and the average 123 mm. of cerebrospinal fluid. The total proteins were calculated in 13 instances with maximum of 45, minimum of 20 and average of 30 mg. per 100 cc.

In 1 instance the protein was elevated (83 mg. %) due to the presence of contaminating blood, subsequent to trauma at the point of puncture. The sugar content was determined in 4 instances and found to be normal (63, 72, 76 and 80 mg. %) and the chlorid content was also normal in 2 cases (696 and 727 mg. %). Excepting the 2 instances in which blood was present due to trauma at the point of puncture, the appearance, red cell count, white cell count, Pandy test, Ross-Jones test, colloidal gold reaction, Kahn and Wassermann were all normal. In these 2 instances the fluid was that of a typical "bloody tap."[15] The cerebrospinal fluid pressure appeared to bear no direct relationship to the presence of the headache. In 10 cases from 0.25 to 0.5 mg. of ergotamin tartrate was given intravenously after the initial pressure reading was made and before any fluid was removed. Eight of these patients were relieved of headache and 2 were unrelieved following the ergotamin, but without any observable relationship to the alteration in pressure of the cerebrospinal fluid. These cases are reported in detail elsewhere.[10]

TABLE 1.—THE CEREBROSPINAL FLUID DURING MIGRAINE HEADACHE.

Case.	Initial pressure, mm. of water.	Cells per c.mm.		Mg. per 100 cc.			See footnotes.
		Red cells.	Lymphocytes.	Protein.	Sugar.	Chlorid (as NaCl).	
CI	40	..	..	..	..	..	2, 4, 5
EG	50	..	..	34	80	727	1, 4, 5
LC	80	1050	4	83	..	..	6, 7
HMc	100	0	0	20	..	..	1
PG	100	5	0	45			
MT	110	..	..	28	..	..	1
BB	110	12	0	24	63	..	2
EE	110	4	0	31	76	696	3
GF	130	0	0	38	..	..	1, 3
VV	145	..	..	39	72	..	1, 5
EG	155	0	0	20	..	..	1
MJ	165	2	3	25	..	..	1
JH	180	292	4	41	..	..	7
EM	180	3	2	27	..	..	1, 3, 5
AH	190	0	0	20			
Averages	123	..	1	30			

There were no neutrophils observed. The Ross-Jones and Pandy tests, colloidal gold reaction, and the Wassermann (or Kahn) tests were negative in all fluids.

1. Given 0.25 to 0.5 mg. of I.V. ergotamin tartrate during the puncture with relief of headache.
2. Given 0.25 to 0.5 mg. of I.V. ergotamin tartrate during the puncture without relief of headache.
3. Increased headache followed an increase of the cerebrospinal fluid pressure.
4. Decreased headache followed an increase of the cerebrospinal fluid pressure.
5. Increased headache followed a decrease of cerebrospinal fluid pressure.
6. Decreased headache followed a decrease of cerebrospinal fluid pressure.
7. Bloody tap.

Between the migraine attacks, 34 punctures were performed in 29 patients (Table 2). The cerebrospinal fluid pressure was measured in 28 instances. The results ranged between 190 and 90 mm. with an average of 139 mm. of cerebrospinal fluid. The cell count

in the fluids varied between 11 and 0 lymphocytes with an average of 2 cells per c.mm. Only one fluid had more than 6 cells per c.mm. The protein content was determined in 27 fluids. The results varied between 80 and 11 mg. % with an average of 29 mg. per 100 cc. Only one fluid had a protein content greater than 45 mg. per 100 cc. and in this case the fluid from a subsequent puncture showed a normal protein content. The sugar content was determined in 7 fluids. The results varied from 114 and 52 mg. with an average of 73 mg. per 100 cc. Only one fluid (from a patient with a mild diabetes mellitus) had a sugar content greater than 100 mg. %. The chlorid content was determined in five fluids. The results varied between 769 and 715 with an average of 739 mg. %. The colloidal gold test was normal in all fluids.

TABLE 2.—THE CEREBROSPINAL FLUID DURING MIGRAINE HEADACHE.

Case.	Initial pressure, mm. of water.	Cells per c.mm.		Mg. per 100 cc.			See footnotes.
		Red cells.	Lymphocytes.	Protein.	Sugar.	Chlorids (as NaCl).	
ED	90	0	0	23			
JH	90	0	0	37			
JD	95	0	5	31			
ER	100	..	5	..	..	..	2
EM	110	0	5	27			
JC	110	9	1	16			
ED	120	1	0	34			
WL	120	0	1				
HM	125	0	0	39			
SG	125	70	0	29			
DL	125	..	4	45	93		
MT	125	0	1	34	52	769	
MT	..	2	11	22	74	758	
JG	125	Bloody	..	..	..	..	2
LK	130	0	0	27			
GS	135	0	0	21			
W	140	0	0	20			
RC	140	630	18	15	..	..	2
SB	150	0	0	43	66		
MW	150	..	5	33			
MT	160	0	1	20	114	733	1
LC	170	12	2	27			
LP	170	0	0	26	..	721	
NMc	175	0	3	11			
MY	180	..	1	80			
MY	..	..	..	45			
GR	180	3	0				
LP	180	0	0	27	..	715	
				22			
RC	185	0	2	15			
MG	190	0	6				
MD	..	0	3				
LM	..	0	2				
MC	..	..	..	26	58		
NM	..	0	1	45	55		
Averages	139	..	2	29	73	739	

There were no neutrophils observed. The Ross-Jones and Pandy tests, colloidal gold reaction, and the Wassermann (or Kahn) tests were negative in all fluids.

1. Mild diabetes mellitus with blood sugar of 200 mg. per 100 cc.
2. Bloody tap. Cell count and protein content not included in averages.

Discussion. As is well known, certain forms of headache are associated with and probably dependent upon an increased intracranial (cerebrospinal fluid) pressure. These are the headaches

associated with brain tumors, congestive heart failure, uremia, "meningitis serosa," post-alcoholic "wet brain," and so forth. Such headaches are often increased by an increase in the intracranial pressure and relieved by a decrease in spinal fluid tension. The cases mentioned by Cushing[16] and Thomas[17] and certain of those reported by Mingazzini[7] fall into this group. Another group of headaches, such as those occasionally following lumbar puncture, are associated with a low cerebrospinal fluid pressure. These are often relieved by increasing the cerebrospinal fluid pressure. Finally there is a large and miscellaneous group of headaches which appear to be independent of the cerebrospinal fluid pressure. It is most likely that the migraine headache falls into this last group.

One of the theories concerning the etiology of migraine implies an increase in the cerebrospinal fluid pressure. This theory postulates a cereb al or meningeal congestion due to toxic or allergic reactions or to intracranial water retention. This congestion is presumed to distend the meninges thus producing headache. If such a congestion occurred it would be expected to produce a measurable increase in intracranial pressure before or during the headache. Our observations with those of Pool *et al.*[10] demonstrate that only rarely is the cerebrospinal fluid pressure elevated in migraine during or between headaches. Our observations also indicate that increasing the cerebrospinal fluid pressure by inhalation of CO_2, jugular compression, coughing and straining, or decreasing it by hyperpnea or the removal of fluid does not consistently alter the intensity of migraine headaches in either direction.

Pickering[18] has observed that the headache following the administration of histamin does not occur until the initial rise of cerebrospinal fluid pressure is disappearing. Similarly, migraine headaches may follow changes in the cerebrospinal fluid pressure which have disappeared before the occurrence of the headache. Other theories suggest that the migraine attack may be due to a localized dilation or spasm of one or more small vessels of the cerebral, pial or dural vascular bed with or without perivascular edema.

Our observations neither add to nor detract from such theories. What observations we have made do suggest the necessity for further observations of the cerebrospinal fluid during the paroxysmal and interparoxysmal periods of "migraine."

Summary. 1. In 15 cases of migraine, the cerebrospinal fluid pressure, measured during a migraine headache, was slightly elevated in 1 case (190 mm. of water), slightly low in 3 cases (40, 50 and 80 mm. of water) and averaged 123 mm. of water.

2. In 29 cases of migraine observed during an asymptomatic interval, the cerebrospinal fluid pressure was slightly elevated in 2 cases (185 and 190 mm. of water), low normal in 3 cases (90, 90 and 95 mm. of water) and averaged 139 mm. of water.

3. In 43 determinations the total protein was normal in all fluids (exclusive of those contaminated by blood) irrespective of the pres-

ence of headache with the exception of 1 case which showed a normal value at a subsequent puncture.

4. In 10 instances, the amount of sugar present in the spinal fluid was within the normal range irrespective of the presence of headache.

5. In 7 fluids the chlorid content was normal.

6. In all cases (44) the Ross-Jones and Pandy tests and colloidal gold reaction were normal except when the spinal fluid was contaminated with blood subsequent to hemorrhage at the point of puncture.

7. The cell count was normal (less than 6 cells per c.mm.) in all but 2 cases which had 6 and 11 cells per c.mm. respectively (bloody fluids excluded).

8. In all of the fluids the Wassermann (or Kahn) test was negative.

Conclusion. We observed no significant abnormality of, nor consistent deviation from the normal cerebrospinal fluid pressure in 44 cases of migraine. The total protein content, cytology and serology of the cerebrospinal fluid were normal. Any significant abnormality of the cerebrospinal fluid renders doubtful a diagnosis of migraine.

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ALLERGY IN MIGRAINE-LIKE HEADACHES.

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There is general agreement concerning the use of the arbitrary term, migraine, to designate those cases of recurrent headaches with their allied symptoms of nausea, vomiting and visual disturbance. Because of the almost purely subjective nature of the findings in this disease, it is not difficult to understand the multiplicity of explanations as to the true etiology of migraine, or the even greater number of widely differing therapeutic procedures recommended to bring about relief. That the underlying cause of this common condition is still obscure is evidenced by such wide differences of opinion as recently offered by Riley,[1] Hartung,[2] Moehlig,[3] Vaughan, [4, 5] Hunt,[6] Foldes,[7] and others.

In Riley's exhaustive study and review of the literature of migraine prior to 1932 but slight mention is made of the possible allergic nature of this disease; whereas various other writers have completely disregarded allergenic factors as being of importance. Although an interrelationship between allergy and migraine has been suspected for some time, it was first emphasized by Vaughan[4] in 1927, and subsequently studied by Rowe,[8] Balyeat and Rinkel,[9] Forman,[10] De Gowen,[11] Diamond,[12] and other more recent writers. Because of the still prevalent wide differences of opinion in this regard it would seem that it might be of value to present additional evidence in support of allergic factors in the genesis of migraine-like headaches.

The material for this study consists of a series of 127 cases which were seen in the University Hospital during the years 1931 to 1934. In all instances the headaches were localized to the frontal region. In 61.4% head pain was unilateral frontal in location, always occurring upon one or the other side. In 26% the attacks were most frequently bilateral frontal. In the other 12.6% of cases the differentiation between the unilateral or bilateral localization of pain was not recorded.

It should be emphasized that the irregularity in regard to the time interval between headaches characterized this series of cases. The individual attacks varied from instances of almost daily occurrence to a frequency of once in approximately 3 months, or upon

the average of every 18 days. The duration of individual seizures ranged from an hour to that of 7 days, an average of 42 hours elapsing between the initial symptoms and the termination of the postmigrainous manifestations.

Visual disturbances were very frequently, although not invariably, associated. In all instances nausea and vomiting had at some time been present.

Those cases in which other central nervous system disease or involvement of the paranasal sinuses occurred were excluded; errors of refraction were previously corrected. The routine study included a careful history and general physical examination. All patients were routinely tested with 96 food extracts and 25 epidermals as prepared by the method of Coca.[13] All testing was done by the intradermal method, using 0.03 cc. of a 1 to 1000 dilution for each injection and employing the skin of the back for the test site. In the majority of instances the entire group of injections was done during one afternoon, the readings were made in 30 minutes and again after 18 hours.

In this group of 127 cases there were 95 females (74.8%) and 32 males (25.2%). The average age at the time the patients were first seen was 37 years, the youngest 17 and the oldest 83. The average duration of symptoms had been 20 years.

Age of Onset of Symptoms. Table 1 shows the age in terms of decades at which time the occurrence of headaches was first noted. Those patients who had the beginning of their symptoms as early as they could remember were included among those in the first decade. It is noteworthy that migraine-like headaches occurred before the age of 16 years in 58% of cases.

Table 1.—Age of Onset of Symptoms in Decades With Percentage for Each Decade.

Years.	Per cent.	Years.	Per cent.
0–10	39.4	31–40	7.1
11–20	33.0	41–50	0.8
21–30	18.9	51–60	0.8

Family History of Allergy. A familial incidence of allergy was found to be present in 81.6%. A maternal atopic background was evident in 58.4% against a paternal allergic history in 33.6% of cases. Included in these two groups 16.8% of patients revealed a bilateral positive family history. Although allergy did not apparently exist in the familial antecedents of the remaining 6.4%, a history of atopy was found to be present on the offspring of these patients. Table 2 shows the specific incidence of these various allergic states said to have existed in these families. Closer analysis showed that migraine was found in 68% of the families: a history in the mother of 48.8%, and in the father in 20%, whereas in 5.6% of the cases both parents had typical recurrent headaches. Migraine existed in the siblings only in the remaining 4.8%.

TABLE 2.—FAMILIAL INCIDENCE OF ALLERGY.

	Maternal (families).	Paternal (families).	Siblings (families).	Children (families).
Migraine	63	27	30	3
Hay fever*	9	11	10	3
Asthma	8	7	10	3
Eczema	4	4	6	4
Urticaria	2	2	4	5

* Includes both seasonal and perennial hay fever.

PRESENCE OF OTHER ALLERGY. In 43 of this group of 127 cases (34%) an incidence of other allergic manifestations was reported as shown in Table 3.

TABLE 3.—OTHER TYPES OF ALLERGY SHOWN BY 127 CASES OF MIGRAINE.

	Cases.
Hay fever*	22
Urticaria	17
Asthma	4
Gastro-intestinal allergy	4
Sensitization dermatitis	3
Angioneurotic edema	1

* Includes both seasonal and perennial hay fever.

CONTRIBUTORY FACTORS, OTHER THAN FOODS, ASSOCIATED WITH THE PRECIPITATION OF HEADACHES. It had been noticed in the routine histories that patients frequently related their sick headaches with a wide and varied group of extrinsic causes other than foods. A total of 78 cases (61%) gave such a history. It may also be noted that the clinical manifestations of migraine would frequently occur entirely independently of these suspected environmental factors. Table 4 lists these associated agents which were reported by the patients as being influential in the induction of their attacks.

TABLE. 4—CONTRIBUTORY FACTORS SUSPECTED BY PATIENTS AS PRECIPITATING HEADACHES.

Menses	30	Worry	3
Emotional upsets	21	Constipation	3
Excitement	13	Eye strain	3
Fatigue	10	Drafts	2
Exertion	7	Colds	2
Nervousness	6	Dust	2
Warm weather	3	Sunshine	1
Cold weather	3	Noise	1
High humidity	3	Too much sleep	1

FOODS SUSPECTED BY THE PATIENTS AS CAUSING HEADACHES. In 47 cases (37% of the total) it was suspected by the patient that the ingestion of certain specific foods had a direct association with the onset of a migrainous attack. Many patients, entirely by their own volition, had learned to eliminate these articles of their diet. In Table 5 are given the 15 most commonly suspected foods in the order of decreasing incidence.

TABLE 5.—ORDER OF INCIDENCE OF SPECIFIC FOODS SUSPECTED BY PATIENTS.

1. Onion	6. Meat	11. Radish
2. Bean	7. Milk-cream	12. Lettuce
3. Egg	8. Cabbage	13. Asparagus
4. Coffee	9. Peanut	14. Cocoa
5. Tomato	10. Strawberry	15. Apple

FOODS DETECTED BY SKIN TESTING. In Table 6 are listed the foods most commonly found to give positive skin reactions. The minor variations from the lists reported by other writers may be due in part to the dietary habits of people living in this particular geographical area.

TABLE 6.—INCIDENCE OF FOODS GIVING POSITIVE SKIN TESTS.

1. Grains (wheat chiefly)	6. Onion	11. Milk-cream
2. Coffee	7. Peanut	12. Tomato
3. Pea	8. Radish	13. Date
4. Celery	9. Cabbage	14. Spinach
5. Berries	10. Cocoa	15. Carrot

SUMMARY OF RESULTS OF TREATMENT WITH AN ELIMINATION PROGRAM. Each patient was instructed upon a rigid elimination plan in which all skin reacting foods and all foods suspected by the given individual as producing symptoms, regardless of the skin reactions, were entirely removed from the diet. In addition all patients were instructed to keep a dietary diary as described by Vaughan.[14] Upon return visits the results of treatment were evaluated and certain suspicious foods were cautiously added to the diet.

Adequate follow-up information was obtained either by direct questioning upon return visits or otherwise by questionnaire in 77 cases (60.6% of the total group). Of this number it was known that all patients followed instructions completely from periods of time ranging between 6 weeks and 4 years, or an average of 8.5 months. Table 7 lists statistically the results from this type of treatment. By "complete relief" is meant those cases having no recurrence of their migraine headaches during the period in which they were followed. "Excellent relief" includes the group in which headaches were of rare occurrence. "Good relief" indicates those in which the number and severity of attacks were reduced to less than one-half, or in which the seizures were distinctly less severe.

TABLE 7.—RESULTS OF TREATMENT.

	Per cent.
Complete relief	18.2
Excellent relief	20.0
Good	14.3
Fair relief	13.0
Little or no relief	33.7

From the above table, 66.3% were at least partially or completely relieved of their recurrent headaches, in contrast to approximately one-third of the cases receiving no benefit.

It is interesting to note that within this group of 77 cases only 47.7% of the male patients were adequately relieved of their symptoms following their specific elimination program outlined, whereas 72.2% of the females received a satisfactory therapeutic result. Vaughan,[5] on the other hand, found a correlation between sex incidence and results exactly opposite to this. Of this series of women patients, those in whom the train of migraine symptoms was frequently precipitated by the occurrence of the menstrual cycle received significantly less relief than in that group in which there was no known association with the menses.

Whether attacks of migraine began before or after the age of 16 years apparently made no practical difference in the general response to treatment. Neither did the length of time the patients had suffered from migraine symptoms seem to alter the final results. In like manner the presence or absence of a positive family history of migraine or other allergy appeared to be in no relationship to the expectancy of beneficial returns. Similarly no statistical importance could be derived from the fact that 73.5% of the patients giving a history of suspicious foods were relieved by treatment, whereas 62.8% of the group without such a history were improved.

There seemed to be some evidence to point toward a slightly better prognosis in those patients who gave a history of other associated allergic manifestations than in the group with negative histories in this respect. In the former 24 cases received relief against 7 who were not benefited. In the series with migraine as the only allergic disease present in the family 26 cases were improved with elimination programs against 20 with no change in symptoms.

Conclusions. A group of 127 cases of migraine-like headache, studied and treated from the allergic point of view, has been presented.

The results of treatment in the 60.8% of patients from whom adequate follow-up information was available showed that two-thirds of this number experienced relief of symptoms, partial or complete, following the rigid avoidance of suspected articles of the diet as determined by skin testing and dietary history.

We believe that allergy is an important contributory factor in certain cases of irregularly recurrent migraine-like headache.

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THE RELATIONSHIP BETWEEN URINARY CREATININ AND TOTAL BODY CREATIN, SURFACE AREA, AND BODY WEIGHT.

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The literature contains many contradictory statements regarding the existence of a relationship between urinary creatinin and body weight, surface area, or other variables. In many of the studies, no account was taken of the influence of the varying quantities of ash, ether extract, and water. Other workers have generally discarded the viscera and skin, and many have not made concomitant determinations of ash, ether extract, and water. Comparatively recent work has shown that the skin contains an appreciable quantity of creatin. In view of these facts, well-controlled experiments have been carried out on rats, in which the comminuted animal, minus the contents of the gastro-intestinal tract, was analyzed for the various constituents.

Body weight was the first variable to be related to creatinin elimination. Folin,[1] in 1904, observed that body weight appeared to be the chief factor determining the amount of creatinin excreted by an individual, and that obese individuals excreted relatively less creatinin per kilo of body weight than lean ones. Then, in 1908, Shaffer[2] stated that "the amount of Kreatinine-nitrogen per kilo—the kreatinine coefficient—shows a direct parallelism with the mus-

cular development or strength, or 'muscular efficiency' of the individual." Muscular development and creatinin elimination were correlated by McClugage, Booth and Evans.[3] Patients exhibiting high creatinin coefficients were well-muscled, while those exhibiting low coefficients were either poorly-muscled or excessively obese. These facts were in general agreement with the observations of Tracy and Clark[4] and also of Hodgson and Lewis[5] that the creatinin coefficients of athletic women corresponded to those of men. These observations indicate that the fat content of the tissues markedly influences the relationship between body weight or tissue creatin and urinary creatinin.

In infants, Daniels and Hejinian[6] found that the relation of the creatinin output to the length of the child gave a more nearly accurate estimate of the physical development than is shown by the creatinin-weight relationship. Beard[7] found that the correlation coefficients between the excretion of creatinin-nitrogen and the body weight, surface area, or height of a large number of students gave little if any evidence for a relationship between these variables.

In 1913, Myers and Fine[8] found in skinned eviscerated rabbits a constant relation existing between total body creatin and daily creatinin elimination, with the urinary creatinin also following the body weight in every case. In this connection it is of interest that Chanutin and Silvette[9] have shown that the skin of rats averaged 0.145% creatin.

Mendel and Rose,[10] in their creatin studies on rabbits, recognized the importance of considering the fat, ash, and water. The importance of these factors was further emphasized by Benedict and Osterberg.[11] Shaffer[12] called attention to the importance of the water and nitrogen content of tissues used in creatin studies. Relatively few workers have considered the possible influence of these factors upon the interpretation of the creatin-creatinin relationship.

It is apparent from this review of the literature that there is a difference of opinion regarding the relationship between urinary creatinin or creatinin coefficient and various body variables.

Experimental. The rats used in these experiments were mature, healthy animals selected from our colony. Each animal was kept on a diet of 20% dried extracted beef,* 15% lard, 46% cornstarch, 5% cod-liver oil, 5% dried yeast, 4% salt mixture (Osborne and Mendel,[13] 3% sodium chlorid and 2% agar, until a constant weight had been reached. The metabolism cage used was similar to that of Levine and Smith.

Urine was collected daily for at least 7 days, and as much longer as was necessary to obtain constant results. Weighings were made daily. The rat was killed by a single blow on the back of the neck. Then through a long midline incision the intestines and stomach were removed quickly, opened, and cleared of the contents. The contents alone were discarded. All urine was expressed from the bladder. The entire rat, minus the gastro-

* Valentine Meat Juice Company, Inc., Richmond, Va.

intestinal ballast, was thoroughly ground and mixed. The samples of tissue were placed in covered dishes and weighed immediately. Creatin determinations were made in triplicate while all others were in duplicate. The creatin was estimated by the method of Rose, Helmer, and Chanutin;[14] the urinary creatinin by the method of Folin;[15] and the total nitrogen by the Kjeldahl method. The fat was determined by extracting with ether in a Soxhlet apparatus the dried tissue residue from the total solid determination. The tissue was incinerated over a low flame for ash.

Surface area was estimated by a modified Meeh-Rubner formula.[16]

$$S = 12.54 \times W^{0.60}$$

S is the surface area in square centimeters and W is body weight in grams. The formulæ used for the correlation coefficient and its probable error were as follows:

$r = \frac{\Sigma xy}{\sqrt{\Sigma x^2} \cdot \sqrt{\Sigma y^2}}$, probable error $= 0.675 \times \frac{1-r^2}{n}$. In the formulæ, Σ stands for summation; r, the correlation coefficient; x, the deviation of any item of the first series from the average of that series; y, the deviation of any item of the second series from the average of that series; n, the number of items.

Organic creatin refers to the creatin in the water-, ash-, and fat-free tissue.

Results. The results of the various analyses are summarized in Table 1. The ash, total solids and nitrogen are quite constant, but the fat varies considerably. These results approximate those of Chanutin.[17]

The average of the creatinin coefficients is practically identical with that of Chanutin and Kinard.[18] The creatinin coefficients were calculated daily and the average values listed in Table 1.

TABLE 1.—BODY CREATIN AND URINARY CREATININ OF THE RAT.

Number.	Dead weight, gm.	Ash, %.	Total solids, %.	Ether extract, %.	Creatin.		Nitrogen.		Creatinin coefficient.	Average daily creatinin, mg.	Total body creatin, mg.	Surface area, sq. cm.
					Wet, %.	Organic, %.	Wet, %.	Organic, %.				
1 ♀ . .	329	3.50	36.1	12.3	0.311	1.53	...	...	16.0	14.4	1004	406
2 ♀ . .	382	3.22	43.4	22.1	0.339	1.88	2.87	16.0	13.6	13.5	1276	444
3 ♀ . .	395	3.41	43.3	21.3	0.300	1.62	2.95	16.2	14.4	14.7	1168	453
4 ♀ . .	317	3.54	40.5	17.0	0.282	1.41	3.19	16.0	14.1	12.1	874	397
5 ♂ . .	469	2.87	42.6	20.4	0.274	1.40	3.15	16.3	13.3	16.2	1263	502
6 ♂ . .	452	3.02	42.8	20.3	0.279	1.43	3.08	15.8	14.4	16.9	1243	491
7 ♂ . .	420	3.22	40.3	16.9	0.315	1.56	3.45	17.1	15.2	16.8	1301	470
8 ♂ . .	382	3.07	43.5	20.8	0.267	1.36	3.14	16.0	12.1	12.6	1010	444
9 ♂ . .	403	3.18	41.4	18.0	0.285	1.40	3.22	15.9	14.0	15.6	1131	459
10 ♂ . .	396	3.46	37.4	13.2	0.308	1.48	3.24	15.6	16.0	16.9	1201	454
11 ♀ . .	329	3.23	47.6	26.6	0.240	1.35	2.81	15.8	13.7	12.3	776	406
12 ♀ . .	269	3.60	40.6	17.2	0.268	1.35	3.06	15.5	15.4	11.2	699	360
13 ♀ . .	248	3.42	42.0	19.4	0.263	1.37	3.15	16.4	14.5	9.6	636	343
14 ♀ . .	272	3.00	41.4	18.6	0.293	1.48	3.07	15.5	13.8	10.2	779	362
Mean . .	...	3.27	41.6	18.9	0.287	1.47	3.11	16.0	14.3	13.8	1026	428

The correlation coefficients are collected in Table 2. There is a good correlation between the average daily creatinin and total body creatin or total body weight or surface area. Perhaps there is a slight relation between percentage wet creatin and creatinin coefficient.

TABLE 2.—CORRELATION COEFFICIENTS.

Total body creatin	and average daily creatinin	(0.892 ± 0.010)
Body weight	and average daily creatinin	(0.904 ± 0.009)
Surface area	and average daily creatinin	(0.906 ± 0.009)
Wet creatin, %	and average daily creatinin	(0.301 ± 0.044)
Organic creatin, %	and average daily creatinin	(0.210 ± 0.068)
Organic body weight	and average daily creatinin	(0.942 ± 0.005)
Total body creatin	and creatinin coefficient	(0.000 ± 0.048)
Body weight	and creatinin coefficient	(−0.170 ± 0.069)
Surface area	and creatinin coefficient	(−0.168 ± 0.047)
Wet creatin, %	and creatinin coefficient	(0.349 ± 0.042)
Organic creatin, %	and creatinin coefficient	(0.093 ± 0.048)

Discussion. Creatinin coefficients are frequently calculated from the average of the daily urinary creatinin and the body weight at the time of death. The value of the coefficient, therefore, depends upon the single weighing of a rather variable factor, body weight. It appears more reasonable to calculate the coefficients daily or to use the average daily weight and average daily creatinin.

It seems that the percentage wet creatin—taking no account of the varying quantities of ash, water, and especially of fat—should bear a less constant relation to the average daily creatinin than does the "organic" creatin. However, this is not the case.

Myers and Fine[8] found in skinned, eviscerated rabbits that the ratio between total body creatin and daily creatinin was the most reliable means of comparing these substances because the factor of body weight is thereby eliminated from the calculations. In the present study, in which the skin, stomach and intestines were retained, the correlation coefficient between total body creatin and average daily creatinin of the rat is (0.892 ± 0.010). This coefficient is slightly lower than those obtained in correlating body weight and surface area with the creatinin elimination.

Myers and Fine also stated that animals with a low percentage content of body creatin exhibited a low creatinin coefficient. Their data only partially confirm the statement, for omitting the two extreme values, the correlation coefficient is only (0.521). In the present study in rats, the correlation coefficient between total body creatin and creatinin coefficient is (0.000 ± 0.048).

In students, Beard[7] found little if any relationship between creatinin excretion and surface area, and between creatinin nitrogen and body weight. Our data indicate that the average daily creatinin is related to both the body weight and surface area, but the creatinin coefficient is related to neither of these variables. The correlation coefficient between "organic" body weight, *i. e.*, the total ash-, fat-, water-free tissue, and the average daily creatinin is (0.942 ± 0.005).

Apparently the total body creatin, body weight and surface area are related to the average daily creatinin, but not to the creatinin coefficient.

Summary. A statistical analysis of data obtained in the rat indicates the existence of a definite relationship between the average daily urinary creatinin and to total body creatin or body weight or surface area.

Apparently there is no relationship existing between the creatinin coefficient and total body creatin, body weight or surface area.

The percentage wet creatin of the whole rat possibly bears a slight relation to the average daily creatinin or creatinin coefficient, but the percentage "organic" creatin bears no relation to these variables.

A very high correlation coefficient was obtained between "organic" body weight and the average daily urinary creatinin.

In all the experiments, the whole animal, excepting the contents of the stomach and intestines, was used for analysis.

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FAILURE OF INTRAVENOUS HYDROCHLORIC ACID TO SHORTEN ANESTHESIA.*

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In view of the widespread interest in the announcement that intravenous injections of N/10 hydrochloric acid promptly terminate anesthesia and because of the great practical value of such a discovery, it was deemed advisable to carry out controlled experiments testing the accuracy of this report.

It seems that Miss Moorman,[1] of Joplin, Mo., having found that intravenous injections of hydrochloric acid terminated anesthesia in animals, told Dr. MacGilvra who, with a Kansas City laboratory, verified the results. The injections were then used successfully in a patient in an emergency. In 7 other instances, anesthesia in patients was terminated by the use of the acid.

MacGilvra[2] reported that the hydrochloric acid injections had accelerated the recovery of rabbits, guinea pigs, rats, monkeys, and 8 human beings under ether anesthesia and 1 human being under avertin anesthesia. No details were given except in the case of the patient under avertin anesthesia. Ellison and MacGilvra[3] later discussed the remarkable recovery of this patient and suggested further probable uses of the hydrochloric acid injections.

Shambaugh and Boggs,[1] however, were unable to accelerate recovery from anesthesia in dogs anesthetized with ether or avertin or nembutal by the intravenous injection of N/10 hydrochloric acid. Neither were they[5] able to shorten the recovery period of guinea pigs, rabbits, dogs, monkeys and baboons from ether, pentobarbital sodium and tribrom-ethanol narcosis. Control animals were used in these experiments.

In view of these differences it was decided to carry out carefully controlled experiments on dogs and rabbits anesthetized with ether, pentobarbital sodium, and paraldehyde[3] to study the effect upon the recovery of the animals following the intravenous injection of N/10 hydrochloric acid.

Methods. Mature, well-nourished dogs and rabbits were used in all experiments. In some cases the animals were subjected to anesthesia several times, but only after a rest of at least 7 days.

* Read before the South Carolina Academy of Science, Columbia, S. C. April 6, 1935.

Pentobarbital sodium (nembutal) was given by inhalation, and the paraldehyde was given by stomach tube. Ether was administered evenly to a point where respiratory failure appeared imminent. The N/10 hydro-

TABLE 1.—ETHER.*

Animal.	Weight, kg.	HCl, N/10 cc.	Attempts to stand, minutes.	Stands, minutes.	Walks, minutes.
Dog	17.6	10.0	10.0	11.0	11.5
"	17.7	10.0	10.0	10.5	11.0
"	6.4	1.5	9.0	10.0	10.5
"	7.3	5.5	7.0	10.5	11.5
"	10.0	10.0	9.0	11.5	12.5
"	9.5	8.0	7.5	12.5	19.0
"†	6.0	0.0	5.0	7.0	7.5
"†	7.4	0.0	4.0	5.5	6.0
"†	16.2	0.0	5.0	7.0	8.0
"†	18.2	0.0	5.0	6.0	6.5
"†	10.1	0.0	19.0	21.0	21.0
Rabbit	2.2	1.0	3.0	9.0	9.5
"	2.3	2.0	4.0	8.5	11.0
"	2.8	2.0	9.0	11.5	20.0
"	1.9	2.0	9.0	14.0	15.0
"	2.7	2.0	5.5	18.0	21.0
"	2.7	2.0	5.0	7.5	8.0
"†	2.7	0.0	4.0	4.2	5.5
"†	1.6	0.0	10.0	11.0	11.5
"†	2.4	0.0	2.5	5.2	5.5
"†	1.9	0.0	4.5	6.5	18.0
"†	2.2	0.0	5.5	8.5	9.0
"†	2.4	0.0	6.5	7.0	8.0

* Administered by inhalation.
† Control.

TABLE 2.—NEMBUTAL.*

Animal.	Dosage, gr.	Weight, kg.	HCl, N/10 cc.	Attempts to stand, hours.	Stands, hours.	Walks, hours.
Dog	7.9	17.9	5.0	5.2	5.5	6.0
"	3.7	8.3	2.5	6.5		
"	7.9	18.0	10.0	9.0	9.8	10.0
"	7.4	16.7	10.0	6.8	8.0	8.0
"	8.2	18.7	10.0	4.0	4.5	4.5
"	8.1	18.4	10.0	3.6	4.6	4.7
			10.0			
"	6.9	15.6	5.0	5.8	6.1	6.1
"†	7.4	16.8	0.0	...	9.5	9.5
"†	8.2	18.6	0.0	5.8	6.0	6.1
"†	4.8	10.8	0.0	...	...	13.0
"†	3.0	6.8	0.0	2.8	3.0	3.2
Rabbit	1.1	1.9	1.0	2.6	2.7	3.2
"	1.4	2.4	2.0	...	3.0	3.0
"	1.5	2.6	1.8	2.2	2.2	2.3
"	1.3	2.2	2.0	1.1	1.7	1.7
"	1.4	2.5	2.0			
			2.0	2.3	2.4	2.4
"†	1.5	2.7	0.0	3.0	3.1	3.3
"†	1.7	2.9	0.0	...	2.5	2.5
"†	1.2	2.1	0.0	...	2.1	2.2
"†	1.1	2.0	0.0	1.2	1.3	1.3

* Intraperitoneal injection.
† Control.

chloric acid was injected slowly into the external saphenous vein of the dog and into an ear vein of the rabbit in amounts varying from 2 to 10 cc.*

TABLE 3.—PARALDEHYDE.*

Animal.	Dosage, gr.	Weight, kg.	HCl, N/10 cc.	Attempts to stand, hours.	Stands, hours.	Walks, hours.
Rabbit	52.5	2.7	2.0	1.0	5.9	6.1
"	46.5	2.4	2.0	4.9	5.9	6.3
"	51.0	2.6	2.0	4.3	6.0	6.1
"†	52.5	2.7	0.0	...	5.0	5.1
"†	48.8	2.5	0.0	3.0	4.1	4.7
"†	48.8	2.5	0.0	5.0	5.5	6.0

* Administered by stomach tube.
† Control.

In nembutal and paraldehyde anesthesia time was measured from the moment the prone animal showed evidences of general relaxation until the animal attempted to stand, stood, walked. In ether anesthesia, time was measured from the moment respiratory failure appeared imminent until the animal attempted to stand, stood, walked.

Groups of animals were anesthetized on the same day in an effort to duplicate all conditions. From the groups, random selection was made of control animals. The control animals were treated exactly like the others except that no hydrochloric acid was administered.

Results. Recovery from nembutal anesthesia or from ether anesthesia in the dog and rabbit was not hastened by the intravenous injection of N/10 hydrochloric acid.

Recovery from paraldehyde anesthesia in the rabbit was not hastened by the intravenous injection of N/10 hydrochloric acid.

Discussion. As in all work of this nature, individual differences in reaction were noted. It is felt, however, that a sufficiently large number of animals was used to justify the conclusions.

Immediately following the injection, the respiratory rate increased, as was expected. However, the recovery period was not shortened, but possibly lengthened.

The experiments were not continued further because no evidence whatsoever was found that the hydrochloric acid hastened the recovery from anesthesia.

Summary. Intravenous injections of N/10 hydrochloric acid do not hasten recovery of dog and rabbit from nembutal, ether or paraldehyde anesthesia. Apparently, such injections tend to lengthen the period of anesthesia.

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* It is not possible to compare the quantities of N/10 HCl used with those of MacGilvra or of Ellison and MacGilvra for these workers gave no detailed data. They mentioned that a total of 8.6 cc. of acid was injected in one patient but no other figures were given. No data were given of their animal experiments.

MULTIPLE MYELOMA WITH HYPERPROTEINEMIA. CASE REPORT.

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Multiple myeloma is a rare disease comprising about 0.03% of all malignancies.[1] Its rarity and consequent unfamiliarity constitute an obstacle to its recognition and account for the "low index of suspicion" among clinicians regarding it. The clinician, confronted by it, is liable to be taken unaware and may fail even to suspect it as a diagnostic possibility. The diagnosis has too frequently been suggested by the radiologist and even the pathologist. Moreover, the range and variety of its clinical manifestations may be confusing. The disease may involve the skeletal, hemopoietic, respiratory, gastro-intestinal and neuromuscular systems. A multiplicity of symptoms and apparently unrelated findings is thus possible and may produce a complex clinical picture difficult, at times, to correlate and interpret. A knowledge of the fundamental pathologic processes entailed, namely tumor growth of hemopoietic tissue with invasion and destruction of bone and bone marrow, is helpful to an understanding of the symptomatology and clinical evolution of the disease. A detailed description of these, however, is beyond the scope of the present report. An excellent one may be found in the fairly recent and exhaustive review of Geschickter and Copeland.[1,2]

Of the diverse clinical features of the disease none is pathognomonic; several, as isolated findings, are highly suggestive of myeloma and in combination are strong presumptive evidence of it. The authors referred to above have summarized the more important of these essentially as follows: (1) Multiple involvement of the skeletal trunk in an adult; (2) pathologic fracture, especially of a rib; (3) the excretion of Bence-Jones bodies; (4) characteristic lumbar pain with signs of early paraplegia; (5) an otherwise inexplicable and increasing anemia of the primary type; (6) chronic nephritis with nitrogen retention and normal or low blood pressure. The significance of the last two as clinical leads to the diagnosis of multiple myeloma is perhaps not sufficiently appreciated. If, when they occur, one fails to recognize them as unobtrusive indications of the disease, he is likely to be confused or even misled by what would otherwise be valuable diagnostic clues. If the findings ordinarily associated with multiple myeloma are absent or inconspicuous

the existence of an unexplained anemia, especially if it simulates the primary type or the occurrence of an unusual nephropathy may give the only clue to the real nature of the disease. These findings should always prompt a search for Bence-Jones proteinuria and other evidences of multiple myeloma.

The reasons for reporting the present case are as follows: (1) The diagnosis of multiple myeloma was first suggested by the existence of an apparently atypical "nephritis" and an unusual progressive type of anemia which at first largely overshadowed the more clinically characteristic but less strikingly evident features of the disease. It illustrates these particular aspects of myeloma, emphasizes their importance from a diagnostic standpoint and conveniently epitomizes the atypical blood and renal findings. (2) A more pertinent reason, however, was the occurrence of a markedly increased concentration of the plasma proteins. Several writers, in recent years, have called attention to a remarkable hyperproteinemia associated with multiple myeloma. The condition is especially interesting from the standpoint of pathologic physiology. However in several instances it has been accompanied by and probably causally related to a variety of unusual and even bizarre clinical phenomena. This is quite apparent in the few cases that have been reported thus far. It is considered worth while therefore to review these briefly and to report our own observations in the present case.

Hyperproteinemia. Hyperproteinemia is decidedly uncommon. Its occurrence has been reported in several conditions other than multiple myeloma. Perlzweig, Delrue and Geschickter[3] and Johansen[4] found instances in the literature in which it was associated with an undiagnosed case with enlarged inguinal glands, with neoplasms, especially large kidney tumors and with certain types of infections, notably kala-azar. The most striking cases, however, have been found in association with multiple myeloma. It has been known for a long time that cases of multiple myeloma may exhibit abnormalities of the plasma proteins.[5] These, in most instances, were attributed to Bence-Jones protein in the serum. However the first case of hyperproteinemia, associated with multiple myeloma was reported by Perlzweig, Delrue and Geschickter.[3] Geschickter subsequently observed a second case.[2] Following their report 15 additional cases have been either reported or referred to in the literature. Bannick and Greene,[6] Peters and Eisenman[7] and Shirer, Duncan and Haden[8] each observed 2 cases. Kumpf,[9] Jores,[10] Johansen,[4] Reimann,[11] Wintrobe and Buell,[5] Bonniger[12] and Cantarow[13] have each reported a case. Reimann[11] also cited an unpublished case of Medes. These instances of hyperproteinemia are all that have been reported or referred to in approximately 500 cases of multiple myeloma in the literature. This, however, affords no basis for conclusions regarding its incidence, for there have been only approximately 35 reported cases of multiple myeloma in

which satisfactory quantitative investigation of the plasma proteins has been carried out. These figures emphasize the inadequacy of our data and the impossibility of drawing reliable conclusions from it.

We know, however, that the concentration of the plasma proteins in multiple myeloma is quite variable, for in more than half the cases in which they have been determined they have been found to be within normal limits or diminished. Considering the loss of protein through the kidney (serum-albumin and Bence-Jones protein) and the malnutrition and cachexia that commonly occur in the course of the disease, Chester[14] regards hypoproteinemia as more consistent with multiple myeloma. He is of the opinion that repeated observations over prolonged periods would reveal a relatively higher incidence of hypoproteinemia even in those cases in which the plasma proteins had previously been high. Such a view, however, is not confirmed in the present case. Repeated determinations disclosed a marked and sustained elevation of the plasma proteins. In fact the last determination, made on the day of exitus, was actually higher than the figures previously obtained. Peters and Eisenman[7] pointed out the lack of correlation between total protein values and the nutritive state in conditions in which globulin is elevated. Hyperproteinemia is entirely compatible with malnutrition, the latter being evidenced by reduction in the albumin concentration. The albumin deficit however may be compensated by excessive increases in globulin.

In the cases thus far reported in which fractional analysis has been carried out the abnormally high concentration of the plasma proteins has been shown to be due either to hyperglobulinemia or actual Bence-Jones proteinemia. Perlzweig, Delrue and Geschickter,[3] Johansen,[4] and Bannick and Greene[6] found high values for euglobulin and less significant amounts of pseudoglobulin I and II. Reimann's[11] case is exceptional in that it showed an excessive concentration of fibrinogen (5.48%). Shirer, Duncan and Haden[8] and Cantarow[13] demonstrated extraordinary amounts of Bence-Jones protein in the serum of their patients. An actual decrease in the albumin concentration occurred in every instance in which fractional determinations were reported. Jacobson[15] reported a case in which 7.8% of Bence-Jones protein was found in the blood. In view of the fact that no entirely satisfactory method has been devised for the quantitative estimation of Bence-Jones protein in plasma, his figures have been regarded with skepticism by most subsequent writers and Perlzweig, Delrue, and Geschickter[3] considered the bulk of the protein in Jacobson's case to have been euglobulin. However, the reports of Shirer, Duncan and Haden[8] and Cantarow[13] tend to support Jacobson's findings. Since the figure for Bence-Jones protein in this particular case represented only part of the total plasma protein the latter undoubtedly was high. In 7 cases, including the present one, Bence-Jones protein was found in the

serum or the urine, while in 5 cases it was not demonstrable in either. Thus hypertroteinemia, in some instances, may be due to an actual Bence-Jones proteinemia. However there still remains a larger group in which evidence of a relationship between the two is doubtful or entirely lacking.

The pathologic physiology of hyperproteinemia and its peculiar association with multiple myeloma are entirely obscure. The fact that it is encountered, at least in its most striking form, in a disease otherwise characterized by the occurrence of abnormal protein (Bence-Jones) is worthy of note and indicates a probable bearing on the question of the origin of the plasma proteins in general. Perlzweig, Delrue and Geschickter[3] have suggested, in view of the fact that Bence-Jones protein is immunologically distinct from the normal blood and tissue proteins, that it may behave as a foreign protein capable of inducing a systemic reaction with hyperproteinemia, such as is observed in animal and immunization experiments. This hypothesis seems untenable as the evidence at the present time indicates that, in some cases at least, hyperproteinemia may occur independently of Bence-Jones protein while in others it is actually due to Bence-Jones proteinemia. Against it also is the fact that Bence-Jones protein ordinarily occurs in the serum or the urine without the production of hyperproteinemia. Reimann[11] interpreted his observations as being in harmony with the theory that the bone marrow is a source of blood proteins. Certainly the association of hyperproteinemia and Bence-Jones protein with disease of the bone marrow is suggestive of more than a casual relationship between them. The suggestion, however, is less impressive when one considers that fibrinogen, a hepatic product, is likewise uniformly increased. Again, Peters and Eisenman[7] have found consistent increases in the serum globulin in association with diseases of the liver, an organ also regarded as a possible source of blood proteins. The meagerness of our information concerning hyperproteinemia does not permit any conclusions as to its cause or significance. The whole subject is vague and requires further elucidation.

Why hyperproteinemia should occur in some cases of multiple myeloma and not in others remains unexplained. Quite as inexplicable is the observation that in some cases it has produced no manifestations by which it might be recognized clinically while in others it has presumably given rise to decidedly unusual and quite variable clinical phenomena. In the cases of Bannick and Greene,[6] Peters and Eisenman,[7] Kumpf[9] and Jores,[10] no mention is made of any unusual findings attributable to hyperproteinemia. In the cases in which Bence-Jones proteinemia was present a precipitate formed in the serum at 56° during inactivation for the Wassermann reaction. Perlzweig, Delrue and Geschickter[3] found it practically impossible in their case, to obtain serum for blood calcium determinations due

to failure of the blood clot to retract. This finding led them to an investigation of the plasma proteins and the discovery of a hyperproteinemia. In Reimann's[11] case the hyperproteinemia was discovered by an inability to count the erythrocytes in the counting chamber due to excessively rapid rouleaux formation. This aroused the suspicion of an abnormality of the blood proteins, most probably an increase in fibrinogen. Autohemagglutination of the erythrocytes was also observed in attempting to obtain a donor for blood transfusion and, likewise, an extraordinarily rapid sedimentation of the erythrocytes. Bonniger[12] also experienced difficulty in counting the red cells in his patient, but in contrast to Reimann's case, the cause was apparently a coagulation of the blood on contact with Hayem's solution. The cells could be counted in physiologic salt solution. This observer also noted that the blood plasma was viscid and sticky and there was a "tendency of the erythrocytes to agglutinate." It is interesting to note that Hopkins and Savory,[16] 23 years ago, were unable to obtain an erythrocyte count in a patient with multiple myeloma on account of too rapid coagulation of the blood. The significance of this was not appreciated at the time. Johansen[4] could not obtain specimens of citrated blood for examination because of abnormal coagulation of the blood. Serum had to be expressed from the clot apparently because the latter failed to retract normally. Only by using excessive amounts of citrate was he able to obtain a blood count. He also failed to obtain a sedimentation rate due to spontaneous agglutination of the cells. Wintrobe and Buell[5] observed spontaneous precipitation of protein which occurred invariably on withdrawal of blood from their patient. The latter presented a very unusual clinical picture in which thrombosis of the retinal veins occurred and circulatory changes in the extremities simulated Raynaud's disease. The present case exhibited the phenomenon of autohemagglutination as noted by Reimann[11] and a remarkably accelerated sedimentation velocity of the erythrocytes. Thus it is apparent that hyperproteinemia of the degree sometimes encountered in multiple myeloma may account for a variety of unusual phenomena. It is therefore of some practical importance to the clinician and to the clinical pathologist to recognize the significance of these and their probable explanation on the basis of hyperproteinemia. The latter should always arouse a suspicion of multiple myeloma.

Case Report. L. P. (No. 180322), a 48-year-old Portuguese male cook, was admitted to the San Francisco Hospital, on the Stanford Medical Service, February 9, 1934, complaining of pains in the back and right buttock of 3 months' duration and bleeding from a tooth socket following extraction of a tooth 1 month previously. His family history was negative. Except for an apparently uncomplicated pneumonia in 1930 he had been reasonably strong and healthy until the onset of his present illness. There was no history of important trauma.

Present Illness. In September, 1933, about 5 months before his present entry, he was admitted to the San Francisco Hospital with a facial erysipelas which cleared up uneventfully in 10 days. He remained well until December, 1933, 3 months before entry. At that time he developed dull pain in the right lumbar region and right buttock. The pain was at first intermittent, non-radiating and not definitely associated with any activity. It gradually became more constant and severe, with occasional sharp exacerbations and aggravated by sudden movements. The pain continued for a month, at the end of which time, although he sought no medical attention, he was compelled to quit work on account of it. Early in January, 1934, he developed pains in the left scapular region, which subsided gradually and spontaneously after 2 weeks. On January 4, 1934, he had an upper tooth extracted, following which he bled profusely and subsequently continued to ooze blood even during his stay in the hospital. Two weeks before entry he had a brief episode of chills and fever which cleared up in about 12 hours but left him with a slight unproductive cough. For a month before entry he was in bed on account of pain, increasing weakness, cough and bleeding from the gums. He had lost about 30 pounds during the 3 months preceding his entry to the hospital.

Physical Examination. At the time of entry he was moderately emaciated and appeared obviously ill. His temperature was 98.8°; pulse, 80 to 100, and respirations, 20. The mucous membranes and nails showed marked pallor. The pupils and extraocular muscles were normal. Both fundi showed several small hemorrhages and the left fundus showed a large recent hemorrhage. No appreciable sclerosis of the retinal arteries, plaques or exudate were seen. The disks were normal. The picture was not at all characteristic of hypertensive neuroretinopathy. Examination of the mouth showed moderate pyorrhea and oozing of blood from the margins of several upper and lower teeth, the patient frequently expectorating bloody saliva. No local or generalized adenopathy was found. The chest was characteristically emphysematous and marked dorsal kyphosis was present. The lower rib margins approximated the pelvic brim. The heart was negative; blood pressure, 118/70 to 120/74. The lungs were apparently clear. The abdomen was negative and no viscera were palpable. The rectum, prostate and genitalia were normal. There was marked tenderness to percussion over the fifth and tenth dorsal spines. Neurologic examination was negative except for weakness of the right hand and definitely increased reflexes in the right upper extremity.

Laboratory Findings. Blood. The blood showed a profound anemia with a color index greater than 1 on the first examination and 1 or slightly less on subsequent examinations. The hemoglobin varied from 40% to 27% and the erythrocytes from 1,900,000 to 1,400,000. The leukocyte count was normal except for one examination which showed a reduction to 3600. The smears constantly showed myelocytes and normoblasts and on one occasion myeloblasts were present. The red cells showed marked polychromasia and moderate poikilocytosis. Of the neutrophils, 43% were of the non-segmented type, while only 9% to 20% were segmented. The average diameter of the red cells was 8.1 and the average volume 108 cu. μ on a single examination. The erythrocytes showed a normal resistance to hypotonic saline solutions. The bleeding, clotting time and retractility were normal. A platelet count was not made but these were scarce in the smears.

Urinalysis. The initial examination of the urine showed a moderate cloud of albumin, 2 to 5 red cells per high-powered field and a moderate number of granular and hyalin casts. Of 2 Addis concentration tests, the first was suggestive of a hemorrhagic type of nephritis with definite proteinuria and a relatively large number of red cells and casts in the

sediment; the second showed much less protein and a smaller number of red cells and casts. The concentrating power was somewhat diminished.

TABLE 1.—BLOOD PICTURE.

Date.	Hemoglobin, %.	R. B. C., millions per c.mm.	Color index.	W. B. C.	Polymorphonuclears, %.	PME., %.	PMB., %.	Myelocytes, %.	Myeloblasts, %.	Lymphocytes, %.	Monocytes, %.	Reticulocytes, %.
2/10/34 . .	40	1.78	1.18	7150	66	1	..	10.0	..	38	10	
2/13/34 . .	33	1.70	0.99	8600	53	..	1	6.5	1.5	25	13	5
2/20/34 . .	39	1.99	1.00	6000	63	1	..	1.0	..	22	13	7
3/ 5/34 . .	30	1.65	0.96	3600	52	..	..	..	..	38	10	
3/ 6/34 . .	27	1.41	0.98									

The *Wassermann test* was negative. The *blood urea* was 43 mg. %. The *histamin test meal* gave normal volumes. The free hydrochloric acid varied from 0 in the fasting contents to 96°, and the total acidity from 25° to 104°.

Roentgen examination showed a compression fracture of the first lumbar vertebra and diffuse osteoporosis of the lower ribs and lumbar vertebræ. Films of the skull, pelvis and extremities were negative.

Diagnosis. Multiple myeloma was first suggested by the peculiar blood picture and evidences of an atypical "nephritis." Although these are by no means constant or pathognomonic features of the disease, their combination should always demand consideration of myeloma. This impression was supported by the persistent and distressing character of the back pain and the finding of Bence-Jones proteinuria. The latter was subsequently repeatedly demonstrable in the urine. The Roentgen ray findings were entirely compatible with diffuse myelomatosis of the spine and ribs. The diagnosis also accounted for the emphysema, kyphosis, the localized tenderness over the spine and the compression fracture of the first lumbar vertebra.

TABLE 2.—BLOOD CHEMICAL FINDINGS.

Date.	Total protein.	Albumin.	Globulin.	Fibrinogen.	Serum Ca.	Diff. Ca.	Inorganic P.
2/20/34 . . .	12.8						
2/23/34 . . .	12.0	1.8	10.2				
2/28/34 . . .	11.41	3.66	8.35	..	12.0	7.7	
3/ 6/34 . . .	..	..	..	..	11.3	..	3.74
3/13/34 . . .	13.5	..	..	0.75			

The protein determinations were done by the Kjeldahl method.

Plasma protein determinations were made in conjunction with blood calcium and phosphorus studies. The latter gave normal values but the total plasma proteins were found to be markedly increased. The results of these and later determinations are included in Table 2. The finding of hyperproteinemia was considered strong confirmatory evidence for the diagnosis of myelomatosis.

Course. Except for some decrease in the severity of the pain, probably attributable to Roentgen ray, the patient's course was characterized by progressive weakness and gradual failure. The anemia was not influenced by iron or liver therapy. He died March 13, 1934. Unfortunately, consent for biopsy or necropsy could not be obtained. Although pathologic confirmation is lacking, it was felt the diagnosis rested on reasonably firm clinical grounds.

Comment. In view of the high globulin and fibrinogen content of the plasma, which are generally regarded as influencing the sedimentation velocity of the erythrocytes, a sedimentation test was done. The red cells settled with striking rapidity and clumping of the cells could be observed macroscopically. The cells settled a distance of 43 mm. in less than 15 minutes and so rapidly that it was impossible to obtain clear-cut interval readings. The normal sedimentation rate for the method would have been 10 mm. or less in 1 hour. For the same reason it was thought that the agglutination of a prospective donor's cells in the patient's serum might possibly be accounted for by excessively rapid rouleaux formation, as observed by Reimann[11] rather than by true incompatibility. A control was done by matching the patient's cells with his own serum. Agglutination of the red cells occurred in the control. Reimann[11] points out that this phenomenon of autohemagglutination or pan-agglutination, does not necessarily indicate incompatibility, and in such instances may occur as a result of rapid rouleaux formation, simulating true iso-agglutination. It can be distinguished from the latter by the fact that true iso-agglutinins may be removed from the serum by absorption and are less influenced by dilution of the serum. The practical importance of this is obvious.

The capricious character of these phenomena is indicated by the fact that despite an increased tendency to agglutination of the erythrocytes no difficulty was experienced in counting the red cells in the present instance. Also, in other cases with comparable increases in globulin and fibrinogen, apparently no unusual phenomena whatever have been observed.[6,7,9,10]

The patient's serum also gave a positive aldehyde test. This test, originally described by Napier[17] is a useful diagnostic test for late kala-azar and is dependent upon an excess of globulin in the serum. The reaction consists in the formation of a white opacity and jellification upon the addition of a few drops of formalin to 0.5 to 1 cc. of serum.

Dr. Garnett Cheney, using a method described by Krogh and Nakazawa,[18] found the osmotic pressure of the plasma to be within normal limits (270 mm. water). This agrees with the observations of others who have made determinations of the osmotic pressure of the plasma in hyperproteinemia.[3,4,7] This is not surprising when one considers the relative molecular size and osmotic influence of albumin as compared to globulin. The former exerts an osmotic

pressure approximately 4 times that of globulin. In the hyperproteinemias thus far observed there has been uniformly a reduction of albumin but the resulting osmotic deficit has been compensated by the hyperglobulinemia.

The peculiar type of anemia and clinical evidences of renal involvement as observed in our patient deserve some comment. Despite the fact that they have been associated with myeloma by various writers their value as aids to the diagnosis is not as yet generally appreciated. Their occurrence is still more likely to puzzle than to help the clinician. To call attention to them again and to emphasize their importance is perhaps not amiss.

While anemia is frequent in myeloma its character is quite variable. In most instances it is of the secondary type and lacks distinctive features. However there occurs occasionally an anemia of the type found in our case which differs from any of the ordinary anemias, either primary or secondary. This is characterized by a relatively high color index in which respect it resembles a primary anemia. It is progressive in its course and apparently uninfluenced by either liver or iron therapy. There is no association with achlorhydria. The leukocyte count is usually normal, any increase in this being usually explicable on the basis of complicating infection. As the anemia increases immature cells may appear in the circulating blood. The smears may show normoblasts, myelocytes and rarely myeloblasts, indicating a rather marked disturbance of the bone marrow with active regeneration. In this it differs from the aplastic type of anemias. There is a tendency for the mononuclear forms to increase. Such a blood picture is not pathognomonic but is sufficiently characteristic of widespread disease of the bone marrow to suggest the possibility of myeloma, especially in the absence of bone metastases from a demonstrable primary tumor.

In view of the recent interest in hyperparathyroidism it may be noted that this possibility was suggested by the Roentgen findings in the present case. The cases observed by Peters and Eisenman,[7] Jores[10] and Reimann[11] likewise simulated the Roentgen picture of hyperparathyroidism or diffuse osteoporosis. Aside from the fact that the Roentgen ray appearance at times may be indistinguishable the two diseases may present certain clinical resemblances.[19] In both, skeletal changes may be prominent and pathologic fractures may occur. Hypercalcemia has been reported in myeloma.[8,10,11] Secondary renal changes may occur in both conditions although these should be differentiated without difficulty. In the present instance the Bence-Jones proteinuria, anemia, hyperproteinemia, normal blood calcium and phosphorus and absence of clinical signs of hyperparathyroidism pointed strongly to myeloma. Biopsy, not obtainable in this case, is of course usually decisive.

Renal complications occur in approximately 70% of the cases

of multiple myeloma.[2] The renal changes may be divided into three groups: (1) Those produced by Bence-Jones proteinuria. This group constitutes the most common and distinctive type of involvement. (2) changes merely incidental and in no way properly attributable to myeloma *per se* or to Bence-Jones proteinuria. Among these are the degenerative vascular lesions which might reasonably be expected in any age group comparable to that of myeloma patients. In this group may be included also true glomerulonephritis and nephrosis, both of which may rarely complicate the disease. (3) pyelonephritis and related urinary tract infections incident to lesions of the spinal cord and consequent bladder paralysis. Amyloidosis may occur as a result of myeloma but tends to have an unusual localization, the kidney involvement being rarely marked.

It is with reference to the first group that the urinary findings in our patient are of interest. The latter were atypical and inexplicable on the basis of any of the usual nephropathies. This fact led to a suspicion of myeloma and the finding of Bence-Jones protein in the urine.

Our ideas regarding the relation of Bence-Jones proteinuria to renal injury have been clarified by the recent investigations of Bell,[20] who confirmed the original views of Bohnenkamp.[21] Bell's work has served to simplify the clinical picture and to establish conclusively the pathologic basis for it. The majority of patients, as observed clinically, have proteinuria and less frequently a variable number and variety of casts in the sediment. The proteinuria may be due to the excretion of Bence-Jones protein or serum-albumin or both. Impaired renal function with retention of non-protein-nitrogen may occur and not infrequently progresses to a terminal uremia. The infrequency of hypertension and its concomitant manifestations in these cases is an important and distinctive feature. Gross hematuria and edema ordinarily do not form a part of the picture. Thus the findings differ significantly from those of a true glomerulonephritis and nephrosis. Bell has demonstrated that the pathologic changes in the kidney consist of tubular atrophy due to obstruction of the tubules by casts of Bence-Jones protein. The injury to the kidney is mechanical and not the result of a direct toxic action exerted by Bence-Jones protein, as some writers have believed.[22] Pathologically it represents a variety of tubular contracted kidney but as Fishberg[23] points out, "it is more closely allied to the hydronephrotic contracted kidney than to the hypothetical end stages of chronic nephrosis."

Summary. 1. A case diagnosed clinically as multiple myeloma with hyperproteinemia is reported and the cases in the literature reviewed.

2. Hyperproteinemia is decidedly uncommon and occurs, in its most striking form, in multiple myeloma.

3. In the majority of instances it has been attributable to hyper-

globulinemia without demonstrable relationship to Bence-Jones protein. In 3 cases it was due to extraordinary amounts of Bence-Jones protein in the serum. In the present case, both globulin and fibrinogen were increased in the blood plasma.

4. Hyperproteinemia may produce unusual and variable clinical phenomena, notably: difficulty in counting erythrocytes; autohemagglutination; markedly accelerated sedimentation velocity of the erythrocytes; abnormal coagulability of the blood and spontaneous precipitation of protein in drawn blood. In the presence of Bence-Jones proteinemia precipitation in the serum may occur during inactivation for the Wassermann reaction.

5. The finding of hyperproteinemia or any of its manifestations should suggest multiple myeloma as a diagnostic possibility.

6. The clinical aspects of the blood and kidney changes in the present case are emphasized and their diagnostic importance indicated. These include (*a*) a severe, progressive, macrocytic anemia with evidences of profound bone-marrow disturbance and active regeneration, unassociated with achlorhydria and refractory to liver and iron therapy; and (*b*) an atypical nephropathy in which impairment of renal function without hypertension is a distinctive feature.

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PARADOXICAL PLEURAL PRESSURES.

THEIR RELATION TO THE KIENBOECK PHENOMENON.

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THE wider application of induced pneumothorax in the treatment of pulmonary tuberculosis in the past two decades has naturally led to a more specific knowledge of the difficulties that may be encountered and complications that may arise in the course of this method of therapy. A vast and instructive literature on the subject now awaits the interested or perplexed. Nevertheless, with the exception of Saugman and Hansen's[1] and Schill's[2] reports, very little has been said about the extraordinary condition occasionally observed in artificial pneumothorax and correctly termed "Paradoxical Pleural Pressures."

Paradoxical Pressures in Pneumoperitoneum. Although Zink[3] claims to have found normal pleural pressure values with the pneumothorax needle in the abdominal cavity, his observations have not been confirmed by reliable workers either in this country or abroad. It is now well known that only paradoxical pressures, *i. e.*, higher pressure values on inspiration and lower pressure values on expiration, are obtained if the pneumothorax needle enters the abdominal instead of the pleural cavity in the course of an inflation.

Orientation in such cases is usually not difficult, because, up to a certain point, the paradoxical pressures remain unaltered in spite of the inflation of a large amount of air. This is due to the fact that the inflated air readily escapes into the general peritoneal cavity. Moreover, the patient may complain of pain in the epigastrium during or immediately after inflation, and classic Roentgen findings of pneumoperitoneum are easily elicited when carefully looked for.

However, in this communication, I shall discuss only those paradoxical pressure values which are obtained with the pneumothorax needle indubitably located within the pleural space which does not, directly or indirectly, communicate with the abdominal cavity.

Genesis of Negative Intrapleural Pressure. It may not be amiss at this time to refer, even though briefly, to the genesis of the normal negative intrapleural pressure and the rôle played by changes in these pressures in pneumothorax in general, and on the homolateral diaphragm in particular.

The negative intrapleural pressure is developed slowly, and is due directly to the fact that the size of the thorax after birth increases more rapidly, and to a greater extent, than the lungs which it holds.[4] To fill this enlarging cavity, the elastic lungs expand as far as the bony thorax will permit. Intrathoracic pressure is the pressure exerted on the mediastinal organs, and is equal to atmospheric, less the opposing tension of the elastic recoil force of the expanded lungs. This pressure is obviously more negative during the inspiratory phase, when the lung is stretched to the maximum capacity of the thorax, and less negative during expiration, when the lung has become smaller, and so partially satisfied its own elastic recoil.

When pneumothorax is induced and the pleura and diaphragm are free from extensive adhesions, the lung retracts, and its own elastic recoil is satisfied in direct proportion to the amount of air inflated, with the result that the intrapleural pressure becomes less and less negative. In such cases, the movement of balance, *i. e.*, the pendular movement of the mediastinal contents and under certain circumstances, the paradoxical movement of the diaphragm may be clearly elicited.[5]

Paradoxical Diaphragmatic Excursions in Negative Pressure Pneumothorax. It is still a moot question as to whether or not paralysis of the diaphragm is an absolute pre-requisite for its paradoxical response. I have often seen a raised or motionless diaphragm in cases with complete pneumothorax. Furthermore, an actual ascent of the diaphragm on inspiration is not infrequently observed in cases where the lung fails to expand appreciably, in the presence of highly negative pressures. This paradoxical response has also been noted by Bittrof.[6]

In none of these cases was there any justification for the assumption that the hemidiaphragm involved had been paralyzed. Wellman[14] proved conclusively that the diaphragm in pneumothorax suffers no paresis. On opening the abdominal cavity of rabbits with induced pneumothorax, he saw waves of contraction in the homolateral diaphragm even if its descent on inspiration was hardly discernible. Moreover, he elicited a current of action from the affected leaf during the inspiratory efforts.

It therefore seems reasonable to assume that the efforts of an

enfeebled diaphragm to descend on inspiration in such cases is more than counterbalanced by the rapidly falling intrapleural pressure, with the result that it is aspirated into the involved hemithorax.

Paradoxical Diaphragmatic Response in Positive Pressure Pneumothorax. That the paradoxical response of the diaphragm in pneumothorax cases which were not phrenicectomized may have a different pathogenicity, has been recently pointed out by Udaone and Vadone.[7] They showed that the basis of the phenomenon is the descent of the diaphragm on expiration in cases with positive pressure during the expiratory phase. At this instant, the diaphragm, on finding itself relaxed, is repelled downward by the positive pressure in the pleural cavity. When it contracts again in the next inspiratory phase, it only rises to the height it attained before the impact of the positive pressure. The ascent during inspiration is therefore apparent rather than real.

Paradoxical Diaphragmatic Response After Phrenicectomy. It is of course different in the case of a paradoxical response in pneumothorax when the homolateral phrenic nerve is severed. Here the inert diaphragm follows the labile mediastinum, and responds in the same fashion as its pendular movement. On inspiration, the lung does not expand rapidly and sufficiently enough to fill the enlarging thoracic cage, with its increasing negative pressure, with the result that the mediastinum (if not fixed) and the diaphragm are sucked into the hemithorax. On expiration, these organs revert to the position they held at rest. The movements just described are not materially influenced by the presence of a moderate pleural effusion.

The Pathogenesis of the Kienboeck Phenomenon. When Kienboeck[8] in 1898 first described the phenomenon now bearing his name, little was known of the pneumodynamics involved. He assumed, and Stembo,[9] Holzknecht,[10] Arensperger,[11] von Muralt,[12] and De la Camp,[13] agreed with him, that the paradoxical movement of the fluid in hydropneumothorax was due to the inversion of the diaphragm into the abdominal cavity because of the weight of the fluid it supported. When, during inspiration the diaphragm contracted, it only became flatter, and so raised the fluid level in the thorax. Later, Kienboeck assumed that the diaphragm was paralyzed, and being inert, it was pushed up by the abdominal pressure which increased because of the inspiratory descent of the normal contralateral hemidiaphragm.

In view of the knowledge now available, neither of these explanations help in the understanding of the *modus operandi* of the Kienboeck phenomenon. It has already been shown that the diaphragm is not paralyzed in ordinary pneumothorax. Moreover, inversion of the diaphragm is of very rare occurrence. I have observed but 1 case in over 600 treated with pneumothorax, and this was a patient

who had a recent phrenic avulsion in the presence of a positive pressure pneumothorax.

As to the rôle of the abdominal pressure in unilateral elevation of the diaphragm in pneumothorax or hydropneumothorax, it has been shown by Wellman that no change in the height of the paralyzed or normal diaphragm takes place on the side of the pneumothorax when the abdominal cavity is opened. Moreover, it can be observed radioscopically that pressure applied to the abdomen fails to push the affected leaf of the diaphragm higher up into the chest.

The Kienboeck phenomenon cannot therefore be explained on the basis of the original assumption, but its mechanism can be easily understood if we consider it under the two categories; with and without paralysis of the diaphragm. (1) When the diaphragm is paralyzed it follows the labile mediastinum by being sucked into the chest cavity during the inspiratory phase when the pleural pressure is negative. When fluid is present, the level naturally rises on inspiration and falls on expiration. Moreover, the inspiratory shift of the mediastinum toward the pneumothorax side diminishes the size of the pleural space and thus helps to raise the level of the fluid it contains. (2) With the diaphragm intact, the phenomenon can be observed if the expiratory pressure is positive or the inspiratory pressure highly negative. As already shown, the basic phenomenon of the former is the descent of the diaphragm due to the impact of the positive pressure, at the moment of its expiratory relaxation. The inspiratory ascent is only apparent. When the positive pressure is removed, a loss of the phenomenon ensues. On the other hand, in the presence of a high negative pleural pressure, and only a small effusion, the diaphragm may actually be aspirated into the chest on inspiration, as has already been shown above.

Paradoxical Intrapleural Pressures. The mechanism involved in the production of the Kienboeck phenomenon is stressed because of its importance in the understanding of paradoxical intrapleural pressures. It must be understood that paradoxical diaphragmatic response and paradoxical pleural pressures are not synonymous. As a matter of fact, they do not occur simultaneously, as suggested by Durien,[15] Hamman,[16] Muralt and others, and they have an entirely divergent pathogenicity. Whether the paradoxical movement is due to a paralyzed diaphragm or not, and whether the intrapleural pressure is positive or negative, contrary to the opinion of Parfitt and Crombie,[17] Samson,[18] and others, the pressure relation in the pleural space remains unaltered; *i. e.*, if it is negative on inspiration, it is less negative on expiration, and when positive on inspiration, it is more positive on expiration.

Table 1 shows a study of 11 cases in which phrenic avulsion was performed to augment the effect of a preëxisting pneumothorax.

It will be noted that the negativity of the inspiratory pressure before inflation is not unlike that found in the average pneumothorax case, and the expiratory pressures are invariably less negative. The final pressures at the completion of the refills in such cases, whether positive or negative, retain the normal relations to each other; *i. e.*, the expiratory pressures are either less negative or more positive than those observed on inspiration. In no case was a paradoxical pressure value observed because of the paralysis of the diaphragm.

TABLE 1.—SHOWING NORMAL RELATION OF INTRATHORACIC PRESSURE VALUES AFTER PHRENICECTOMY IN 11 CASES WITH INDUCED PNEUMOTHORAX. PRESSURES ARE IN CUBIC CENTIMETERS OF WATER.

Name.	Sex.	Age.	Pnx. induced.	Side.	Phrenicectomy.	Pressure before inflation.		Pressure after inflation.	
						Insp.	Exp.	Insp.	Exp.
S. T.	F.	29	7–14–29	R.	1– 3–30	−2	+3	−1	+7
A. L.	F.	16	7–24–29	R.	3– 3–30	−6	−4	+7	+9
A. N.	F.	19	10–21–30	R.	1– 7–31	−8	−4	+4	+6
Y. S.	F.	28	7– 6–30	R.	6–11–31	−5	−3	+5	+8
M. F.	F.	17	4– 3–31	R.	8– 3–31	−5	−3	−3	−1
E. T.	F.	28	2– 5–31	L.	4– 3–32	−4	−2	+8	+10
R. M.	F.	32	5– 4–32	R.	4–13–33	−4	−1	+7	+12
L. K.	F.	21	7–20–33	L.	10–10–33	−7	−3	−3	−1
J. S.	M.	34	10–20–31	R.	6–12–34	−5	−3	−2	−0
F. M.	F.	32	6–21–33	R.	10–12–34	−5	−3	+3	+5
J. G.	M.	37	3– 6–34	R.	6–21–34	−5	−3	+1	+2

TABLE 2.—PARADOXICAL INTRAPLEURAL PRESSURES IN 4 CASES TREATED WITH PNEUMOTHORAX.

Patient.	Age.	Sex.	Side.	Pnx. induced.	Pressure before inflation.		Pressure after inflation.	
					Insp.	Exp.	Insp.	Exp.
J. S.	25	M.	L.	12–20–27	−6	−2	+16	+12
M. V.	30	F.	R.	9– 4–25	−8	−4	+24	+20
P. F.	29	F.	L.	5– 4–31	−8	−4	+18	+12
A. B.	25	M.	R.	8–13–26	−12	−6	+20	+16

However, in a study of over 600 pneumothorax patients, 4 were found who exhibited unequivocal paradoxical pressure values. In none, as has already been stated, was there the slightest possibility of the needle having entered the abdominal cavity. In none was there a high position of the diaphragm on the side treated. The paradoxical readings have thus far been obtained in 1 case for 4 months, in 2 cases for 2½ years, and in 1 case for over 5 years. No untoward symptoms were observed, and the collapse therapy was

continued in one until its successful termination, and 3 are still receiving inflation.

In none of these were paradoxical pressure readings obtained while the intrapleural pressure was still negative during the early part of the refill. They were noted only when the pressure values in both inspiration and expiration had become positive during inflation. Weinstein, working with Muralt,[12] has had similar experiences.

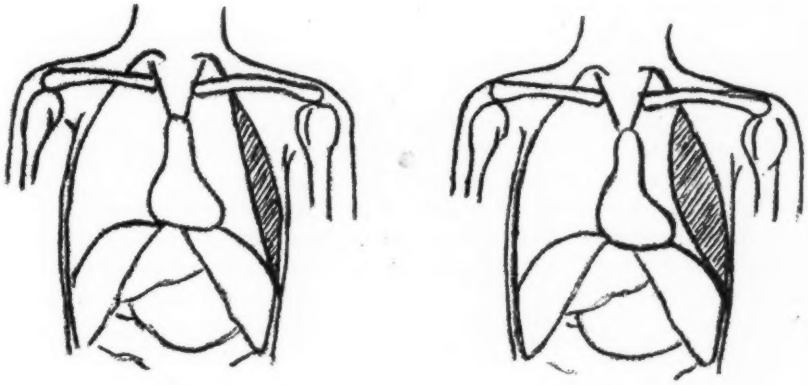

FIG. 1.—(*A*) Size of pneumothorax pocket decreased because of the stretched pleural limiting membrane in inspiration. (*B*) Size of pneumothorax pocket increased in expiration when this membrane is relaxed.

The patients showing paradoxical pressure values had a limited pneumothorax, and in all of them fluoroscopy and occasionally radiography disclosed extensive band-like adhesions with a pleural limiting membrane bound to or near the diaphragm below and to the upper part of the chest above. The diaphragm on the treated side was usually bound down by adhesions. The most important feature in these cases was the pleural limiting membrane, which had a convexity toward the mediastinal aspect of the hemithorax. This was best observed fluoroscopically.

It appears that on inspiration after the limited pleural space has been distended by the inflated air under positive pressure, the rising ribs and the descending diaphragm, when its function is not completely destroyed by adhesions, pull on the more or less convex limiting membrane and straighten it out sufficiently to decrease the size of the pneumothorax pocket. The tension of the air enclosed must necessarily rise at that moment. The converse is true during expiration, when the ribs descend and the diaphragm rises to its former position. This permits the limiting membrane to relax and assume its original mediastinal convexity. The size

of the pneumothorax pocket is thus increased and a fall in the pressure of the air it contains inevitably follows.

Summary. 1. The negative value of the intrapleural pressure is due to the fact that the thorax after birth increases more rapidly and to a greater extent than the lungs it holds. It is equal to atmospheric pressure minus the elastic recoil power of the lungs. This pressure is more negative on inspiration, when the lungs are stretched to the maximum capacity of the expanded thorax and less negative in expiration, when the lungs have become smaller and so partially satisfied their elastic recoil.

2. Paradoxical pressure, *i. e.*, less negative values on inspiration as compared with expiration, may be obtained if the needle, instead of entering the horax, finds its way into the abdominal cavity.

3. Paradoxical intrapleural pressure and paradoxical response of the diaphragm do not occur simultaneously and have an entirely divergent pathogenicity.

4. Persistent paradoxical pleural pressures were obtained in but 4 cases among the 600 treated with induced pneumothorax. They were observed only in limited positive pressure pneumothorax.

5. The most important feature in these cases was the pleural limiting membrane which had a convexity toward the mediastinum. On inspiration, the ascending ribs and descending diaphragm straighten this membrane sufficiently to decrease the size of the pneumothorax pocket, thus increasing the tension of the air it contains. On expiration, the relaxed limiting membrane assumes its original mediastinal convexity, thereby enlarging the pneumothorax pocket. A fall in the pressure of air contained must necessarily follow.

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FAMILIAL PURPURA.

REPORT OF TWO CASES.

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IN addition to thrombocytopenic purpura and hemophilia, another group of "bleeders" has been described. These patients give a familial history of bleeding and show an unusual group of blood findings characterized by prolonged bleeding time, normal clotting time, and normal number of platelets. The clot usually retracts but this may be somewhat delayed. Unlike hemophilia, the disease is found in both sexes and may be transmitted by either parent.

The tendency to bleed appears early, is relatively mild, and becomes less severe after adolescence. The most common forms of hemorrhage are epistaxis, bleeding from the gums, and tendency to bruise easily. The literature, however, affords illustrations of practically every known form of bleeding.

Kehrer[1] in 1876 first called attention to this condition; he was followed in 1881 by Hutchinson[2]. No further cases were reported until Hayem[3] discussed 3 in 1900. Thirteen years later Austin and Pepper[4] reported 1 case. Since then the literature has contained many references to this disease (5 to 24).

In order more successfully to study these conditions some exhaustive experiments have been made as to methods and apparatus. We lack space for details but should mention the painstaking work of Morawitz and Jürgens,[20] Jürgens,[21] Jürgens and Naumann,[22] and von Willebrand.[23]

Recently we have observed two negro boys, brothers, suffering from this hemorrhagic tendency. The bleeding was of the usual type and both patients suffered at times from secondary anemia. The bleeding time was usually prolonged. The platelets appeared to be normal and only once were they found to be low. In one the retractability of the clot was delayed; in the other it was normal. The clotting times remained always within normal limits. We were not able to demonstrate positive tourniquet tests. In both boys the tendency to bleed is gradually diminishing.

Case Reports. CASE 1.—D. M. (No. 255087), a 9-year-old negro boy, was first admitted to this hospital on February 21, 1923, complaining of bleeding gums.

There was no family history of hemorrhagic diathesis. His younger brother (whose case is described in detail below) had at this time shown no signs of bleeding. One brother and 2 sisters had died in infancy of unknown causes.

Only illness was measles in early infancy.

The parents stated that from babyhood the patient had bled from the gums, and following any injury. Epistaxes frequently accompanied head colds, and after severe hemorrhages hyperpnea had been noticeable. During the year previous to admission, tarry stools had been observed.

He had been in the hospital (Wilmington, N. C.) 9 months previous to entry for weakness and shortness of breath. He improved rapidly after transfusion. For the following 9 months bleeding from the gums had been constant.

Physical Examination. A thin boy, moderately ill. Weight, 64 pounds. The cervical glands were moderately enlarged. Marked pallor of the mucous membranes and nail beds. Fundi were normal. The gums were ecchymotic, with some fresh oozing. Caries of the teeth. The tonsils were moderately enlarged. The lungs were clear. The heart enlarged to the left, and a rough systolic murmur was heard over the precordium, maximum at the apex, and transmitted to the axilla. The blood pressure was 112/70. The spleen was not palpable. The urine was normal.

Blood: hemoglobin, 41%; red blood cells, 3,720,000; white blood cells, 6200; with normal differential count. The red blood cells showed central pallor. The blood platelets were 200,000 per c.mm. The clotting time was 9 minutes, control 2 minutes. The patient bled freely for 30 minutes, after which the bleeding was stopped by pressure. The fragility of the red cells was normal. The blood Wassermann reaction was negative. Blood culture: no growth. Roentgen ray and fluoroscopy of the heart revealed moderate enlargement.

The patient remained in the hospital about 2 weeks, improved somewhat, but the gums continued to bleed, local applications of thromboplastin giving only temporary relief.

During the next 2 years that the patient was followed in the medical clinic, the red cell count varied from 3,350,000 to 4,240,000; the hemoglobin from 46 to 56%; the white cell count from 1850 to 7050. Platelet count was 306,000. Bleeding from the gums, though variable in severity, was almost continuous. Thromboplastin was applied to the gums with variable success. Once two petechial hemorrhages were noticed in the conjunctiva of the left eye.

On February 2, 1925, the patient was readmitted because of severe bleeding from the gums.

The physical findings were much as on his previous admission. He weighed 89½ pounds. Pallor was marked. The teeth were dirty. There

were two small ecchymotic areas on the buccal mucous membrane which bled on pressure. There was moderate general glandular enlargement. The spleen was palpable.

The urine was normal; the stool negative for occult blood. Hemoglobin, 30%; red blood cells, 1,800,000; white blood cells, 3800 with normal differential; platelets, 40,000; clotting time, 4 minutes; bleeding time, more than 35 minutes.

He received 3 direct transfusions, the amount of blood varying from 350 to 500 cc. Fibrinogen and thromboplastin were applied to the gums. Except for a brief transfusion reaction the course was afebrile throughout. The gums continued to bleed, but on discharge the hemoglobin was 50%, the red cells, 3,100,000.

After being followed for 3 months in the dispensary, the patient disappeared for 5 years.

During the interval before his third admission, May 6, 1930, he had visited St. Luke's Hospital, and the Morrisania Hospital (both in New York), and received 6 transfusions. In the 9 months previous to entry he had lost 21 pounds, was weak, pale and inactive. The gums bled constantly, and evening rises of temperature had been common. The day before admission he had a mild epistaxis.

On examination the boy appeared to be acutely ill, dyspneic and drowsy. Temperature was 104°, pulse 128. The mucous membranes were almost white. The fundi were normal, eyelids slightly edematous. The gums were pale, hypertrophic, and soft, with a marked tendency to bleed. Lungs: scattered râles at the lung bases. The heart was markedly enlarged with accentuated pulmonic second sound and a systolic murmur, as formerly observed. The liver was slightly enlarged, spleen just palpable.

Hemoglobin 9% (this is very low for accuracy. The next day, after a transfusion of 700 cc., the same observer made it 24%); red blood cell, 1,370,000; white blood cells, 6350, with normal differential; the red cells showing marked variation in size and shape. The platelets were 380,000; bleeding time, 10½ minutes; clotting time, 6 minutes, with a retractile clot. No sickle cells were found in a wet preparation. The fragility of the red cells was normal. No increase in the serum bilirubin. Blood calcium 9.7 mg. per 100 cc. The urine and stools were normal.

After being afebrile for 3 weeks, he developed a lobar pneumonia (right lower lobe). The predominant organisms in the sputum were hemolytic staphylococcus aureus, and streptococcus viridans; no tubercle bacilli found. The leukocytes rose to 15,000 with 89% neutrophils. Recovery was uneventful. He received 6 direct transfusions: one of 500 cc. the others of 700 cc. each.

While the bleeding never stopped entirely, some improvement was noticed after each transfusion. Local treatment of the gums was unsatisfactory. The red blood cells rose to 3,410,000; the hemoglobin to 55%. The bleeding time varied from 2½ to 10 minutes. The platelets varied from 190,000 to 380,000, except for one count of 40,000.

The patient was discharged after 2½ months.

The next 2½ months were characterized by striking improvement. The weight rose to 133½ pounds. Hemoglobin, 82%; red cells, 4,300,000. Efforts to have some much needed dental work done were frustrated by his mother. Moderate bleeding continued. Liver extract and iron ammonium citrate were prescribed.

His fourth admission (October, 1930) was for severe bleeding from the gums. A stay of only 10 days was uneventful. The red cells varied from 3,100,000 to 4,000,000; the hemoglobin from 66 to 68%, the bleeding time was more then 30 minutes, the platelet count 300,000. The physical and laboratory findings were unchanged.

During the 4 years that have elapsed since his last admission the patient has been followed in the dispensary. Bleeding from the gums has been intermittent, though never severe. The mother has never permitted much dental work to be done. Iron ammonium citrate has been given almost continuously, the hemoglobin has varied from 50 to 90%; the red blood count from 3,800,000 to 5,000,000; the clotting time from 2 to 5 minutes; the bleeding time from 1½ to 9½ minutes; and the platelets from 101,000 to 263,000. He has grown and matured normally. His weight was 151 pounds when last seen. He is now over 21 years old.

CASE 2.—O. M. (No. 254687), the brother of Case 1, was first admitted to this hospital on May 8, 1930. He was 15 years old, and had been bleeding from the gums for 8 or 9 days.

In childhood he had measles, mumps, and scarlet fever. Always had epistaxis with a cold. He had grown normally and at the time of admission was in high school. In December, 1928, he was admitted to St. Luke's Hospital, New York, with a history of hematuria and of slight bleeding of the gums (an abstract of this admission was very kindly furnished us by St. Luke's Hospital). The urine on admission showed gross blood. Roentgen ray of the kidneys were negative. The Wassermann reaction was negative. Hemoglobin, 86%; red cells, 4,500,000; white cells, 6800, with normal differential; platelets, 170,000; bleeding time up to 20 minutes, clotting time from 5 to 6½ minutes. One transfusion of 250 cc. Recovery was uneventful, and the boy left after a month.

Ten days before admission to Presbyterian Hospital he had developed a head cold which was accompanied by vomiting and by a severe nose bleed. A day or two later his gums began to bleed; this continued up to the time of entry. Just before admission he had anorexia, frequent vomiting, moderate epigastric pain, occasionally tarry stools and increasing pallor. His left ear had been discharging for 6 weeks.

Physical Examination. A colored boy, aged 15, moderately ill. Temperature, 100.8°; weight, 115 pounds. Marked pallor of the mucous membranes and of the nail beds. There was a purulent discharge from the left ear. The gums were hyperplastic, pale, friable and bleeding. Teeth were in fair condition, some gingivitis. Tonsils large with prominent crypts. Moderate enlargement of the heart, and systolic murmur could be heard over most of the precordium. Liver edge palpable, two finger-breadths below the costal margin. The spleen was just palpable.

The urine was normal. The Wassermann reaction negative. Hemoglobin, 30%; red blood cells, 2,230,000; white blood cells, 8100, with normal differential. Platelets, 260,000. Bleeding time very greatly prolonged, clotting time was only 3 minutes, retraction of the clot did not begin until after 20 hours. The fragility of red cells was normal. The serum bilirubin was normal. The guaiac test on the stool was 1+. The blood calcium was 10.3 mg. per 100 cc. Hemolytic streptococci were grown in pure culture from the gums.

Two days after admission a direct transfusion of 700 cc. was given. Treatment included ferric ammonium citrate and liver extract. He ran fever for 10 days. The gums improved strikingly, after 16 days they bled very little, red cells rose to 4,180,000, with a hemoglobin of 55%.

During the next 2½ years he was seen infrequently in the dispensary. The hemoglobin varied from 89 to 95%, the red cells from 4,800,000 to 5,100,000. Bleeding time from 5½ to 3 minutes; clotting time remained normal. Moderate oozing from the gums continued. He gained from 117 pounds to 161 pounds. The boy matured rapidly and improvement in his general condition seemed to keep pace with this gain. He visited the dental clinic frequently. The bleeding from the gums was not severe enough to interfere with this work. During this period his hemoglobin varied from

58% to 82%, his red blood count from 4,100,000 to 5,100,000, and his platelets from 169,000 to 238,000. On one occasion his bleeding time was 8 minutes, his clotting time 1½ minutes.

He has not been seen in the clinic since May, 1933.

In reviewing these 2 cases we feel no elation because of gratifying results. Although both boys grew and developed normally, when last seen both had hemoglobins in the neighborhood of 50%; in other words, our therapy left much to be desired. We feel justified in thinking some of the responsibility rests with the patients. As example of their mental attitude and lack of coöperation we mention one instance that is noteworthy: they could never go to the dentists when the moon was full, because at such time the bleeding was worse!

Comment. In adding 2 cases to the already large group, it is not our intention to attempt a new classification, or to propose a new etiology.

A review of the literature reveals many cases which fit into a definite pattern, characterized by an hereditary bleeding tendency, associated with prolonged bleeding time. The clot retraction is generally delayed or absent while the clotting time and platelet count are both within normal limits. The hemorrhagic tendency may be transmitted by either parent to children of either sex.

The fact that some of the cases have shown thrombocytopenia, but are linked to this group by their familial characteristics, demonstrates the absence of distinct borderline between this disease and true purpura hemorrhagica. The occurrence of a similar type of bleeding in female members of families, the male members of which have had hemophilia, suggests a possible link with that disease. On the other hand, sporadic cases in every way similar to the disease we are describing have occurred in which no family history of bleeding could be found.

Most of the evidence points to a functional insufficiency of the platelets as the etiologic agent. Definite morphologic changes in the platelets have been noted.

In one group of cases recently described, the platelets were morphologically normal, but were unable properly to agglutinate and produce a normal clot. The final word regarding the etiology has certainly not been written.

In view of the generally good prognosis, therapy should aim to control the immediate hemorrhage, and to combat the resultant secondary anemia.

For both purposes transfusion has proved a valuable weapon. Hemostatic substances applied locally are of doubtful value. General measures such as adequate rest when bleeding is severe, removal of foci of infection, and liberal doses of iron and liver seem to help materially. Irradiation of the spleen may be of value, but splenectomy is definitely contraindicated.

Summary. 1. Two cases have been described of a familial, chronic, hemorrhagic diathesis; with prolonged bleeding time, but with normal clotting time, and normal platelets.

2. The term "Hereditary Thrombasthenia" is usually employed to describe this syndrome, but recently "Constitutional Thrombopathy" has been suggested.

3. Treatment should be conservative: symptomatic local therapy and measures to combat the anemia. Splenectomy is contraindicated.

4. The bleeding tendency usually manifests itself in infancy or childhood. If the patient successfully passes through what may be termed the critical stage (up to 15 years), the prognosis is excellent.

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BOOK REVIEWS AND NOTICES

THE KIDNEY IN HEALTH AND DISEASE. Edited by HILDING BERGLUND, M.D., Stockholm, Sweden. Formerly Chief of the Department of Medicine at the University of Minnesota, and GRACE MEDES, PH.D., Research Biochemist in the Lankenau Hospital Research Institute, Philadelphia. With the Collaboration of G. CARL HUBER, M.D., Professor of Anatomy and Director of Anatomical Laboratories and Dean of the Graduate School of the University of Michigan, WARFIELD T. LONGCOPE, M.D., Professor of Medicine in the Johns Hopkins University, Baltimore, and ALFRED N. RICHARDS, PH.D., M.D., Professor of Pharmacology in the University of Pennsylvania, Philadelphia. Pp. 754; 163 illustrations. Philadelphia: Lea & Febiger, 1935. Price, $10.00.

THIS volume represents a collection of papers on normal and pathologic function and structure of the kidney. Nearly all of these papers, most of them now in revised and amplified form so as to bring them up to date, were originally presented by 41 clinical and laboratory investigators at a symposium which took place in Minneapolis during the summer of 1930.

The subject matter of the book is divided into six parts: Anatomy and physiology of the kidney (Chapters 1 to 9); clinical aspects of renal functions (Chapters 10 to 17); Bright's disease and various other pathologic renal conditions (Chapters 18 to 26); albuminuria and edema (Chapters 27 to 36); ocular changes in Bright's disease (Chapters 37 and 38); and clinical aspects of Bright's disease (Chapters 39 to 44).

The work contains a wealth of information and will be of much value to students of the kidney. Of particular excellence is the part dealing with kidney function. In no other book is there gathered in such accessible form so complete a survey of renal physiology by men largely responsible for the advances made; it must suffice to cite as examples the papers by Richards, Marshall, Rehberg, Homer Smith and White. The various tests for renal function and the pathologic physiology of renal insufficiency form the contents of the second part of the book. Further examples of outstanding contributions are the papers of Longcope and his associates on the part played by streptococci in the establishment of nephritis, by Leiter on nephrotic edema, and several papers by Franz Volhard who together with Fahr laid the foundation of the modern concept of Bright's disease.

B. L.

DAS EXTREMITÄTEN-, THORAX- UND PARTIAL-ELEKTROKARDIOGRAMM DES MENSCHEN. Eine Vergleichende Studie. By PROF. DR. FRANZ MAXIMILIAN GROEDEL, Direktor des William C. Kerckhoff-Herzforschungs-Instituts zu Bad-Nauheim. Band 1: Text (358 pages; 334 illustrations); Band 2: Atlas with 200 Plates. Leipzig: Theodor Steinkopff, 1934. Price, Rm. 25.

THE author, the well-known former director of the Nauheim Institute, but now writing from New York, tells us that after almost 25 years of study he has succeeding in isolating the "Partial-electrocardiograms" of the left and right heart. Though still lacking postmortem confirmation of his clinical studies, he regards this monograph as the first fruit of this new method.

These partial electrocardiograms are given as quite different from Lewis' dextro and levograms for reasons that cannot be detailed, much less evaluated, here. Einthoven's triangle of forces is also rejected in theory, though occasionally used for practical didactic purposes. As an example of the lines of approach eight critical points on the heart are selected with the aid of special, movable "Tastelectroden." Increased distance from points 1 to 4 (in the right ventricle) or 5 to 8 (in the left) indicate delay in excitation spread; an abnormally high site for points 2 or 6 indicate increased speed of spread and so on. The monograph aims to demonstrate that the electrocardiogram records the result (summation or neutralization) of lines of potential developed simultaneously in the two ventricles. Its form therefore, is influenced by the amount of rotation of the heart as well as by the direction of its anatomical axis, and cannot be taken as an expression of the course followed by the contraction impulse. The dextro-electrocardiogram appears normally to have large R and S waves, the sinistro-electrocardiogram a q wave (synchronous with the R of the right ventricle), a large R (synchronous with the right S) and a slightly delayed T.

These are indeed weighty considerations for cardiac specialists and students of the cardiac mechanism. If the author is correct, and his great experience entitles him to the most careful consideration, much that is now accepted by cardiologists will have to be revised. It is hardly necessary, then, to recommend to serious students of the subject the careful study of this book that its text requires. E. K.

RECENT ADVANCES IN ENDOCRINOLOGY. By A. T. CAMERON, M.A., D.Sc. (EDIN.), F.I.C., F.R.S.C., Professor of Biochemistry, Faculty of Medicine, University of Manitoba; Biochemist, Winnipeg General Hospital. Pp. 406; 55 illustrations including 2 plates. Second edition. Philadelphia: P. Blakiston's Son & Co., Inc., 1935. Price, $5.00.

IT is not surprising that the extensive and productive studies in this important field have required a new edition of this book in the short space of 2 years. Especially has the pituitary, with its numerous interrelationships, been a fallow field, so that some 78 pages are required to cover its "recent advances" with due regard for a proper background. The parathyroids, of course, have assumed more important proportions, while the hypoglycemic phases of insulin action also require more space than ever before. The pineal, on the other hand, gets but scant notice and Rowntree's thymic precocity was apparently included at the last moment. Collip's antihormones and the complicated topic of endocrine interrelationships are conservatively handled in Chapter 9. When today's newly discovered facts are crowding so much of the medical knowledge of yesterday either to the scrapheap discards or to the uninteresting category of truisms, such well-digested surveys as this should prove highly useful to the physician who continues to be a medical student. E. K.

THE HARVEY LECTURES. Series 29. Delivered under the Auspices of The Harvey Society of New York, 1933–1934. Under the patronage of the New York Academy of Medicine. By Doctors R. E. DYER, W. M. CLARK, R. G. HARRISON, E. A. DOISY, E. A. GRAHAM, C. L. STREETER, T. M. RIVERS and D. W. BRONK. Pp. 262; illustrated. Baltimore: The Williams & Wilkins Company, 1935. Price, $4.00.

THIS volume is preceded by a short, but singularly penetrating, minute on the death of the President of the Society, Alfred Hess. The eight lectures here collected are of an unusually high quality even for this series. No one

could contest the modest statement in the Preface as to "the distinguished rôle which they fill in Medicine in New York City." Distinctions would be invidious between such sterling presentations as Dyer's typhus fever, Clark's oxidation-reduction systems, Harrison's heteroplastic grafting in embryology, Doisy's estrogenic substances, Graham's clinical studies of the biliary tract and of the pancreas, Streeter's morbid processes in the fetus, Rivers' filterable viruses and Bronk's nervous mechanism of cardiovascular control. E. K.

FAILURE OF THE CIRCULATION. By TINSLEY RANDOLPH HARRISON, M.D., Associate Professor of Medicine, Vanderbilt University School of Medicine, Nashville, Tenn. Pp. 396; 60 figures and 22 tables. Baltimore: The Williams & Wilkins Company, 1935. Price, $4.50.

THE conventional title of this book covers a fresh, important approach to an old problem—namely, the study of such hemodynamic states as "the dyskinetic syndrome" by modern methods that are still apt to be more familiar to the physiologist and biochemist than to even the well-trained clinician. The author's training in and use of these methods, combined with his predominant interest in the clinical problems, peculiarly qualifies him for a study which has led to new interpretations of a number of the clinical manifestations of heart disease. In "hyperkinetic" conditions the author includes such conditions as the overactive or soldier's hearts and those cases where "the physiologic subjective and objective phenomena of circulatory activity appear in exaggerated form." In the "hypokinetic" group are the various shocks and collapses of acute circulatory failure with decreased response. "Dyskinetic" refers to conditions of or leading to congestive heart failure, *i. e.*, hardly more specific than "organic heart disease." The attempt is made to bring the general circulatory disturbances (not including angina pectoris, which is regarded as a local disturbance) into these three categories. The author has attained a good measure of simple clearness without dogmatism. Thus many problems, unanswerable to-day, are left unanswered. However, Hope's "back-pressure" hypothesis of cardiac failure and oxygen lack in the heart muscle as the underlying functional disturbance in angina pectoris and coronary thrombosis are clearly supported. Thyroidectomy in the treatment of heart disease is presented but regarded as too recent to be evaluated—altogether a fresh, sane, useful book. E. K.

MAIMONIDES (THE RAMBAM). THE STORY OF HIS LIFE AND GENIUS. Octocentennial Edition. By DR. J. MÜNZ. Translated from the German, with an Introduction, by HENRY T. SCHNITTKIND, PH.D. Pp. 238. Boston: Winchell-Thomas Company, 1935. Price, $1.50.

THE accompaniment of the two earlier persecutions of the Jews by the incorporation of their best thoughts in the Bible and the Talmud respetively have suggested to the anonymous promoters of the "Jewish Bookshelf" that the present "persecution" should be accompanied by a third collection including the best thoughts of the past 1500 years. This account of Maimonides, coming appropriately on his 800th anniversary, is the first of the series. The 100 books ranging from philosophy to fiction, that are to be published at the rate of 5 volumes a year, should constitute a treasure house of value to Jew and Gentile alike.

This highly eulogistic account of Moses ben Maimon is properly concerned chiefly with his rôle as a philosopher and religious commentator. We read also of his life in the Jewish community in Egypt, where his family settled after being driven from Spain to North Africa and the Holy Land, and of his

display of practical qualities of leadership in raising their intellectual standards and bringing together the warring factions of Judaism. This leadership, it seems, descended in his family for more than 10 generations. As court physician to the Sultan Saladin, his medical side came into prominence. Though trained in the Arabian school, he seems to have been a worthy follower of Hippocrates, using reason based on experience as his guide. The cure should be as simple as possible; the best one can do is to help Nature by fortifying the patient's strength; alcohol is bad for the young but food for the old (one of his 22 rules of hygiene in the *Mishneh-Torah*). Of the 8 medical treatises referred to, we would note especially his book on Psychiatry, called forth by his treatment of the Sultan Almalik's melancholia, and his Epitome of Medicine, a summary of Galen and of the history of medicine up to his time. On reviewing his colorful and versatile life, we agree that he stands out with Richard and Saladin as a 12th century leader and as one of the greatest Jews of the Christian era.

E. K.

SOME NOTABLE EPIDEMICS. By H. HAROLD SCOTT, M.D., F.R.C.P. (LOND.), D.P.H., D.T.M. and H. (CAMB.), F.R.S.E., Assistant Director, Bureau of Hygiene and Tropical Diseases. With a Preface by W. W. JAMESON, M.A., M.D., F.R.C.P., Barrister-at-Law, Professor of Public Health in the University of London; Dean of the London School of Hygiene and Tropical Medicine. Pp. 272. Baltimore: William Wood & Co., 1934. Price, $4.75.

THE careful manner in which this work was planned raises it well above a mere account of various "classical" English epidemics which are not to be found in Hirsch, Hecker or Creighton. Twenty-two epidemics occurring since 1850 have been selected both to illustrate particular landmarks in public health work (such as the first use of chlorine as a water disinfectant or of pasteurization of milk) and to demonstrate how specialists viewed epidemics in pre-bacterial days. A chronological order has been largely followed, with occasional exceptions in order better to compare epidemics caused by the same mode of conveyance (water, milk, food, contact and so on). It is indeed surprising how the keen insight of John Snow, for instance, could grasp the essentials of cholera spread in 1854, and outline steps to be taken which have been but little improved since his day. Eleven of the epidemics were of typhoid, both water and milk borne, and from infected oysters; 5 of scarlet fever; and 3 of Sonne's dysentery, the last of which occurred in 1933. Though of chief interest, in fact a virtual necessity, to students of public health, these "detective stories" should make interesting reading for most anyone, and profitable reading as well for most any physician.

E. K.

A TEXTBOOK OF BIOCHEMISTRY. Edited by BENJAMIN HARROW, PH.D., Associate Professor of Chemistry, The City College, College of the City of New York, and CARL P. SHERWIN, M.D., SC.D., DR.P.H., LL.D., Member of the Staff of St. Vincent's Hospital, and French Hospital, New York. Pp. 797; 52 illustrations. Philadelphia: W. B. Saunders Company, 1935. Price, $6.00.

THIS book, written by 30 specialists in various fields of biochemistry, is an excellent survey of present-day knowledge. Aside from subjects usually included in textbooks on biochemistry there are chapters on the physicochemical properties of the living cell, on the chemical processes concerned in resistance and immunity, and on the chemistry of bacteria. The articles throughout the book give evidence of careful condensation of subject matter; the essentials are clearly and thoroughly presented; for those who

would go deeper there are extensive and well-selected lists of references. Some of the chapters dealing with broad subjects (as for example those on the carriage of blood gases, and on oxidations and reductions) conclude with well-written summaries which should prove of particular help to the non-specialist. The editors and contributors are to be congratulated on providing a book which will serve as a good text for the student and as a modern reference volume for the trained worker in medicine, chemistry and biology.

B. L.

THE TREATMENT OF RHEUMATISM IN GENERAL PRACTICE. By W. S. C. COPEMAN, M.A., M.B., B.CH. (CANTAB.), M.R.C.P. (LONDON), Hon. Physician, B.R.C.S., Clinic for Rheumatism, Peto Place; Assistant Physician, West London Hospital, Children's Department and Hospital of St. John and Elizabeth, etc. With a Foreword by SIR WILLIAM HALE-WHITE, K.B.E., M.D., F.R.C.P., HON. LL.D., Consulting Physician to Guy's Hospital, etc. Pp. 228. Second Edition. Baltimore: William Wood and Co., 1935. Price, $3.25.

THIS survey of the numerous methods of treatment used in the various "rheumatic" diseases is remarkably informative and inclusive. To the American physician, whose skepticism about many remedies especially the proprietaries has progressed further than his British cousins, some recommendations may appear uncritical. However, the author's wide experience must be held in mind and his general attitude of optimism in handling these difficult cases—each as an individual and not by rule of thumb—will be useful to many a perplexed practitioner who has the good fortune to have this book fall in his hands.

E. K.

ALLERGISCHE DIATHESE UND ALLERGISCHE ERKRANKUNGEN. By HUGO KÄMMERER, M.D., Professor at the University of Munich; Chief Physician of the Division of Internal Medicine of the Nymphenburger Krankenhaus, Munich, Germany. Pp. 359; 4 illustrations. Second edition, enlarged and improved. Munich: J. F. Bergmann, 1934. Price, Paper, Rm. 26; Bound, Rm. 29.60.

THIS is undoubtedly the best, indeed the first adequate, German text dealing with present-day views of this rapidly developing field. In addition to an extensive clinical and investigative experience the author brings to his subject a wide knowledge of its literature and a sound judgment in evaluating the material. The allergist will find the work a valuable addition to his library, and German-speaking practitioners as well as allergists should consider it indispensable. (Inadvertently the author cites Coca, Walzer and Thommen's "Asthma and Hay Fever in Theory and Practice" as a British, not an American, publication.)

R. K.

DEUTSCHE VOLKSMEDIZIN. Wissenschaftliche Heilkunde und Kultur. By PAUL DIEPGEN, O. Prof. Dr. Med. et Phil., Berlin. Pp. 136; 7 illustrations. Stuttgart: Ferdinand Enke, 1935. Price, Geh. Rm. 6.—; Leinen geb. Rm. 7.40.

FOLK medicine, which persists to a surprising and unappreciated extent in all civilized countries, is regarded by the well-known author of these lectures as a particular appropriate study in times of need and sickness, when "art, science and reason so often leave us in the lurch." The historical relationships of the magic and religious needs of the German common folk to scientific medicine and to culture in general are well brought

out in 9 chapters that cover semichronologically the whole of German folk medicine from prehistoric to modern times. The influence of commerce and racial combination with surrounding countries is objectively considered; anti-Jewish measures are traced back to 692! The crusades, the medieval pandemics of body and mind, printing, Paracelsus and Mesmer are important landmarks on the progress toward a modern goal that the author regards as a desirable combination of the good to be found in both folk and scientific medicine. E. K.

GESCHICHTE DER PHYSIOLOGISCHEN CHEMIE. By DR. FRITZ LIEBEN, Privatdozent an der Universität Wien. Pp. 741. Wien: Franz Deuticke, 1935. Price, M. 20.

THIS work, the first comprehensive history of physiologic chemistry in English, is a studious compilation of detailed information, with an entirely factual presentation. The obvious effort to produce an all-inclusive work—an effort which for physiologic chemistry is almost futile even in the space of 700 large pages—has resulted in a distinctly textbook appearance. This impression is strengthened by the inclusion of countless organic structural formulas, the citation of last-minute researches and the absence of any portraits which might have served to relieve the reader.

From the standpoint of history, the ancient phases, for a book of this size, appear slighted. No effort has been made, for example, to look critically into the history of urea. The credit for the discovery is given to Rouelle the younger, whereas Boerhaave and probably Pott deserve the plaudits in this connection. Far too sketchy also is the author's treatment of "methods," which have always played an undeniably important rôle. Historically, the development of proper blood sugar methods is as important as the discovery of insulin.

In spite of these criticisms, perhaps unavoidable in a pioneer work, much information has been gathered and stored. The work may well serve as a source of reference and as a starting point for future critical histories of the subject which will no doubt appear. D. D.

MEDIZINISCH-CHEMISCHE BESTIMMUNGSMETHODEN. Eine Anleitung für Studierende der Medizin und für Laboranten. By KARL HINSBERG, Vorsteher der Chemischen Abteilung des Pathologischen Instituts der Charité, Berlin, Privatdozent an der Universität, Berlin. Volume 1. Darstellung der allgemein gebräuchlichen und der wichtigsten quantitativen Methoden. Pp. 93; 29 illustrations. Berlin: Julius Springer, 1935. Price, Rm. 4.80.

THIS small volume is apparently the first part of a work on chemical methods to be used in a hospital laboratory. The first half presents the most used and important general methods and instruments, such as balances, centrifuge, titration, indicators, colorimeters, nephelometers, photometers, polarization, refractometers, gas analysis, blood sampling and nitrogen determinations. In the second special part, the various inorganic (calcium, chlorids, gastric contents, urinary ammonia, alkali reserve) and organic methods are given both in principle and in details of technique. The organic chapter covers hemoglobin, total and residual N, uric acid, bilirubin, blood sugar, cholesterin, acetone, diastase and so on. Much is sacrificed to attain a brief handiness; for non-Germans greater convenience will doubtless be found in works in English, even though larger and more complete. E. K.

TREATMENT BY DIET. By CLIFFORD J. BARBORKA, B.S., M.S., M.D., D.Sc., F.A.C.P., Instructor in Medicine, Northwestern University Medical School, Chicago; Formerly Consulting Physician, The Mayo Clinic. Pp. 615; illustrated. Philadelphia: J. B. Lippincott Company, 1934. Price, $5.00.

A PRACTICAL presentation of the subject for the general practitioner. Part I deals with diet requirements in health. In Part II is described the technique for working out the details of a diet prescription as to quality and quantity, with some useful data on comparative servings of various foods. This part is rather well illustrated. In Part III the diet indications in various diseases are taken up, with a brief theoretical discussion and numerous diet lists. Parts IV and V include lists for routine hospital diets, tube feeding; a number of food, weight and other tables; recipes.

R. K.

LA VIE MÉDICALE AUX XVI^{E}, XVII^{E} ET XVIII^{E} SIÈCLES. By DOCTEUR PAUL DELAUNAY, Membre de la Société Francaise d'Histoire de la Médicine. Pp. 556; 114 illustrations. Paris: Editions Hippocrate, 1935. Price, 40 francs.

THIS thoughtful survey of medical life in the three most important centuries of French history is the fourth production of the Collection "Hippocrate." (Those that have already appeared are: "Acupuncture et médecine chinoise vérifiées au Japon," by T. Nakayama; "l'Atomistique," by M. Boll; "Joseph Le Bon," by Y. Dhotel.) This "para-medical" collection aims to include a wide variety of topics—essays on medical doctrines, the relations of medicine to her sister sciences, medical history, psychologic studies and so on.

If the present volume is a true guide, the series should prove interesting and valuable. Here we have presented by an accomplished medical historian chapters on each of the various aspects of medical life; preparatory, private, professional, corporate, religious, political, social, intellectual and doctrinal. Though the story is limited to France, the author offers such a wealth of colorful detail that the sequential flow of the narrative sometimes is impeded. The factual gain, however, more than recompenses, especially as it is reinforced by copious illustrations and a full index of names. The absence of a subject index is the more keenly felt.

E. K.

CLINICAL LABORATORY METHODS AND DIAGNOSIS. A Textbook on Laboratory Procedures with Their Interpretation. By R. B. H. GRADWOHL, M.D., Director of the Gradwohl Laboratories, Gradwohl School of Laboratory Technique, and Laboratories, St. Louis County Hospital, etc. Pp. 1028; 328 text illustrations and 24 color plates. St. Louis: The C. V. Mosby Company, 1935. Price, $8.50.

THIS is one of the most complete and practical books of its kind that we have had the good fortune to meet, and, as one should expect from a Director both of laboratories and a school of laboratory technique, unmistakably clear and concise directions are given for the most varied methods. In few books of this kind, for instance, would one find 15 paragraphs on the Culture of Sterile Maggots for Use in Therapy, with accurate directions for care of eggs, breeding of larvæ and fly colonies and so on. To the blood, that "ganz besondere Saft," is rightly given the major space—262 pages—so that, as well as the customary items, such matters as platelet counting, Schilling hemograms and so on can be treated in some detail. As perfection is as desirable as it is unattainable, attention may be called to the antiquated classification of chronic renal disease, the omission of Wiseman's

diluted plasma method of estimating erythrocyte resistance, the obsolete clinical evaluation of direct and indirect van den Bergh tests, and the fallacious weak point in Wright's platelet theory (platelets should not be expected in the bone marrow, as the pseudopods break off *in* the vascular channels). Surprising also is the anachronistic reference (p. 933) to Prof. W. G. MacCallum of Columbia! Other slips could be detailed, but they are relatively trifling in a book that conveys such a wealth of accurate information, well presented and copiously illustrated. Especially pleasing are the 24 color plates, expensive items which have almost disappeared from American medical periodical literature. Fifty pages of the blood findings in various diseases should be especially useful to the practitioner. Chapters on autopsy methods, tissue technique, preparation of museum specimens and toxicologic technique add further to the value of this excellent production. E. K.

THE EVALUATION OF SYMPTOMS. Offered After Fifty Years in Medicine. By OLIVER T. OSBORNE, M.A., M.D., F.A.C.P., Professor of Therapeutics, Emeritus, and formerly Clinical Professor of Medicine, Yale University. Pp. 163. New Haven: Yale University Press for the Author, 1935. Price, $3.50.

IMPRESSED by the present-day dependence on laboratory methods, the author aims to emphasize the importance of history taking and the study of symptoms. We do not believe, however, that this laudable purpose is to be advanced by the method here followed. A single page on "The Germs of Infection" and the disease they cause can only be trite and incomplete, while the subsequent pages on "Reportable Diseases and Quarantine," and a later section on "Dieting," are irrelevant. A long chapter on "Symptoms of Disease," arranged alphabetically, occupies three-fourths of the book; but this also fails in its aim. Starting with three conditions (acetonuria, agranulocytosis, albuminuria), for which the reader is referred to other pages, the list soon reaches "blood." Here in 12 pages, anemia, monocytes, platelets, chlorosis, leukocytosis, pernicious anemia, leukemia and so on are touched upon in a random and necessarily inadequate manner that does not emphasize the value of the study of symptoms and may deflect the reader from more statements elsewhere. We can only hope, then, that in another edition the author will recast his text so as to bring out more forcibly the valuable lesson for the present generation that lies in the proper evaluation of symptoms. E. K.

THE TREATMENT OF FRACTURES. By DR. LORENZ BÖHLER, Director of the Hospital for Accidents, Vienna; Lecturer on Surgery in the University of Vienna. Pp. 578; 1059 illustrations. Fourth English edition, translated from the fourth enlarged and revised German edition by ERNEST W. HEY GROVES, M.S., M.D., F.R.C.S., Consulting Surgeon, British General Hospital; Emeritus Professor of Surgery, University of Bristol, etc. Baltimore: William Wood & Co., 1935. Price, $12.00.

"IN main essentials the fourth German edition, of which this is a translation, follows the same lines as those of the third. . . . . The new material in the English edition deals: (1) With the anatomic conditions and the treatment of fractures and fracture-dislocations of the cervical spine, which have been revised in the light of recent experience. (2) In the chapter on medial fractures of the neck of the femur, the recent developments of Sven Johansson's method and the use of two sets of Roentgen ray apparatus for the orientation of the wire guides have been elaborated, because it has been found that in this way the operation is simpler, quicker and more accurate.

As the results of the treatment of fractures depend not merely upon the use of certain appliances and methods, but even more largely upon the education of the surgeon and the organization of the clinic, an Appendix has been added dealing with this important aspect of the problem. For the sake of simplicity, certain other subjects have been relegated to appendices, so as not to break the main theme of the treatment of fractures. These deal with statistics, normal and abnormal movements of the knee-joint, and the nature and treatment of deformities of the foot." (From the Translator's Preface.)

EMOTIONS AND BODILY CHANGES. A Survey of Literature on Psychosomatic Interrelationships 1910–1933. By H. FLANDERS DUNBAR, M.D., PH.D., Departments of Medicine and Psychiatry, Columbia University. Pp. 595. New York: Columbia University Press, 1935. Price, $5.00.

THIS volume represents the combined labors of Dr. Dunbar and her collaborators under the auspices of the Josiah Macy, Jr., Foundation in the collection and recension of contributions published in the last quarter century dealing with the interrelations of the emotions and the body. The text is divided into three principal parts. Part One, "Orientation and Methodology" presents a critical review of the current psychologic concepts and of the experimental approaches in the fields of biology, internal medicine and medical psychology, to the problem of psychosomatics. Part Two, "Organs and Organ Systems," is devoted to the task of orienting the abstracted materials "relating to their meaning in the various fields of medicine, being, however, a key to the available literature rather than a comprehensive or critical survey." Part Three addresses itself to the "Therapeutic Considerations and Concluding Remarks." A bibliographic list of 2251 references corresponding to the divisions of the text occupies 121 pages. In addition there are complete subject and name indices. The scope of the bibliography alone represents an achievement possible only through the organized efforts of a subsidized group; a task beyond the capacity of the individual, who cannot hope to keep abreast of the ever mounting volume of current literature related to the subject, and especially to have a knowledge of the literature from the foreign sources, of which in this book 50% are in German and 6% in other foreign languages.

One notes the beginning transition of medical thought from the mechanistic tradition to the *organismal* theory involving the new concept of the *organism-environment* equilibrium, the concept of the total personality in terms of health and disease. In the sense of Bleuler's dictum that "a physician who thinks in terms of psychogenesis will never become an agent in pathogenesis," this corpus of new thought should widen the perspective and understanding of the physician confined in practice to the single organ or organ system. This volume has much to offer the physician to the end that he no longer contribute to his patient's irremedial invalidism. The author wisely cautions against the overemphasis of psychotherapy in special practice: in the approach to these problems the exclusive emphasis of the psychic is as narrow as that which holds that every psychic disturbance is purely physical in origin. The profession is at the threshold of a new discipline in which there is room for both the conservative and the doctrinaire.

This book fulfills a twofold purpose: first, as an invaluable reference work for the specialists in the fields of psychiatry, neurology and of psychosomatic interrelationships, and second, as a treasury of stimulating information for the practitioner to whom the current literature pertaining to this subject is inaccessible. The book is especially recommended to the young physician. Dr. Dunbar and her collaborators deserve commendation for their prodigious and timely labors in contribution to one of the most vital and vexations of problems. P. R.

NEW BOOKS.

Clinical Laboratory Methods and Diagnosis. A Textbook on Laboratory Procedures with Their Interpretation. By R. B. H. GRADWOHL, M.D., Director of the Gradwohl Laboratories, Gradwohl School of Laboratory Technique, and Laboratories, St. Louis County Hospital, etc. Pp. 1028; 328 text illustrations and 24 color plates. St. Louis: The C. V. Mosby Company, 1935. Price, $8.50. (Review, p. 275.)

A Bibliography of the Poem Syphilis Sive Morbus Gallicus, by Giorolamo Fracastoro. By LEONA BAUMGARTNER, and JOHN F. FULTON. Pp. 157; 9 illustrations. New Haven: Yale University Press, 1935. Price, $5.00.

Maimonides (The Rambam). The Story of his Life and Genius. Octocentennial Edition. By Dr. J. MÜNZ. Translated from the German, with an Introduction, by HENRY T. SCHNITTKIND, PH.D. Pp. 238. Boston: Winchell-Thomas Company, 1935. Price, $1.50. (Review, p. 271.)

International Clinics. Vol. 2, Forty-fifth Series, 1935. Edited by LOUIS HAMMAN, M.D., Visiting Physician, Johns Hopkins Hospital, Baltimore, with 14 Collaborators. Pp. 327; many illustrations, some in colors. Philadelphia: J. B. Lippincott Company, 1935.

The outstanding articles in this number offer survey (Prognosis in Heart Disease, Pneumonokoniosis, Headache, Anemia, Heart Pain, Pyuria in Childhood, etc.) rather than present original evidence.

Indian Journal of Pediatrics, Vol. 2, No. 7 (April, 1935). Edited by Dr. K. C. CHAUDHURI, with 11 Collaborators. Pp. 65; illustrated. Published quarterly in Calcutta. Price, Annual Subscription, Rs. 6/–; Single Number, Re. 1/8.

An Outline of Immunity. By W. W. C. TOPLEY, M.A., M.D., F.R.C.P., F.R.S., Professor of Bacteriology and Immunology in the University of London. Pp. 415; 37 illustrations, 63 tables. Baltimore: William Wood & Co., 1933. Price, $6.00.

The Evaluation of Symptoms. Offered after Fifty Years in Medicine. By OLIVER T. OSBORNE, M.A., M.D., F.A.C.P., Professor of Therapeutics, Emeritus, and formerly Clinical Professor of Medicine, Yale University. Pp. 163. New Haven: Yale University Press for the Author, 1935. Price, $3.50. (Review, p. 276.)

La Vie Médicale aux XVI^E, XVII^E et XVIII^E Siècles. By DOCTEUR PAUL DELAUNAY, Membre de la Société Française D'Histoire de la Médecine. Pp. 556; 114 illustrations. Paris: Éditions Hippocrate, 1935. Price, 40 francs. (Review, p. 275.)

Diet Control. A System of Eleven Hundred Diets for the Prescription of Diabetic, Anti-obesity and Measured Diets in General. By GEORGE E. ANDERSON, M.D , Attending Physician to The Brooklyn and The Lutheran Hospitals; Chief of Metabolic Clinic, The Brooklyn Hospital, and PAUL CHADBOURNE ESCHWEILER, M.D., Assistant Attending Physician to The Brooklyn and The Methodist Episcopal Hospitals; Senior Physician, Metabolic Clinic, The Methodist Episcopal Hospital, New York: Gallo & Ackerman, Inc., 1935. Price, $3.50.

The Depopulation of Pacific Races. Bernice P. Bishop Museum Special Publication 23. By S. M. LAMBERT. Pp. 42; 11 illustrations and 19 tables. Honolulu: Bishop Museum Press, 1934. Price, $1.00.

The Woman Asks the Doctor. By EMIL NOVAK, M.D., F.A.C.S., HONORARY D.SC. (DUBLIN); Associate in Gynecology, Johns Hopkins Medical School; Former Vice-President American Gynecological Society. Pp. 189. Baltimore: The Williams & Wilkins Company, 1935. Price, $1.50.

Some Thoughts of a Doctor. By FREDERICK PARKES WEBER, M.A., M.D., F.R.C.P., F.S.A. With a Preface by SIR W. LANGDON BROWN, M.A., M.D., F.R.C.P., Regius Professor of Physic in the University of Cambridge. Pp. 183. London: H. K. Lewis & Co., Ltd., 1935. Price, 6s.

The Problem of Mental Disorder. A Study Undertaken by the Committee on Psychiatric Investigations, National Research Council. Members of the Committee: Madison Bentley, Chairman, Sage Professor of Psychology, Cornell University; E. V. Cowdry, Professor of Cytology, Washington University. Pp. 388. New York: McGraw-Hill Book Company, Inc., 1934. Price, $4.00.

The Proceedings of the Charaka Club, Vol. VIII. Post Multa Virtus Opere Laxare Solet. Pp. 202; illustrated. New York: Columbia University Press for the Charaka Club, 1935. Price, $5.00.

The Spleen and Resistance. By DAVID PERLA, M.D., Associated Pathologist and Bacteriologist, Montefiore Hospital, and JESSIE MARMARSTON, M.D., Associate in Pathology, Cornell University Medical College. With a Foreword by DAVID MARINE, M.D., Pp. 170. Baltimore: The Williams & Wilkins Company, 1935. Price, $2.00.

The Story of Medicine in the Middle Ages. By DAVID RIESMAN, M.D., Sc.D., Professor of the History of Medicine and Professor Emeritus of Clinical Medicine, University of Pennsylvania; Member, History of Science and Medieval Academy of America. Pp. 402; illustrated. New York: Paul B. Hoeber, Inc., 1935. Price, $5.00.

Clinical Tuberculosis, in two volumes. Edited by BENJAMIN GOLDBERG, M.D., F.A.C.P., F.A.P.H.A., Associate Professor of Medicine, University of Illinois College of Medicine, etc. With the Collaboration of 33 Contributors. Pp. 1580; illustrated with over 640 half-tone and line engravings and 9 full page color plates. Philadelphia: F. A. Davis Company, 1935. Price, $22.00.

Krebs im Licht Biologischer und Vergleichend Anatomischer Forschung. By MED. DR. JOSEF LARTSCHNEIDER, LINZ A. D. DONAU. 11 Band, 2 Heft: Adenomkrebs Kystom Scirrhus Bindegewebe Mesenchym Sarcom Odontom Kieferkystom. Pp. 197; 57 illustrations. Wien: Franz Deutsche, 1935. Price, M. 7.

NEW EDITIONS.

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PROGRESS
OF
MEDICAL SCIENCE

SURGERY

UNDER THE CHARGE OF
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PILONIDAL SINUS.

HARDLY any condition in the field of minor surgery is so little understood either as to the exact nature or treatment as is that of pilonidal sinus. It has been the subject of many articles in the surgical literature of the past 10 years and it is commonly seen and recognized in every good surgical clinic. However, it is apparent that among general practitioners the condition is not commonly recognized or understood, since so frequently the surgeon sees the patient after the lesion has been repeatedly treated as a simple abscess and multiple incisions have been made to drain the contents.

The lesion is also called sacrococcygeal cyst, sacrococcygeal fistula, sacrococcygeal sinus and pilonidal sinus, the latter term having been given it by Hodges[1] because of the nest of hair so frequently found within the sinus. Anderson,[2] in 1847, reported a case of a 21-year-old man who had a "scrofulous sore" over the sacral region following a blow over the area 6 months previously. On examination there was a very small sinus, too small to admit a probe. There was an abscess present which was opened and later fine, soft hair was removed from the wound. J. Mason Warren[3] reported 3 cases before the Boston Society for Medical Improvement in 1854. His description is so clear that it merits recording in this review: "Abscess, containing Hair, on the Nates—Dr. J. Mason Warren had met with three cases of abscess of the nates connected with a fistulous opening over the coccyx, containing hair. The last case is a type of the two others. The patient, a young man, 20 years old, had for some time suffered from an irritation on one of the nates. Finally, an abscess formed and broke, followed shortly by one on the opposite side, both being the sources of great discomfort, the first having become fistulous. On separating the nates, Dr. W. at once discovered, about an inch below, in the median line and over

the coccyx, a small aperture, about large enough to admit a probe, looking like a pit in the skin, and lined with epidermis. A probe, being introduced, penetrated to the depth of an inch and a half.

"From his experience in the two former cases, Dr. W. was at once able to say that it led to a cavity containing hair, which was probably the origin of the abscess in the neighbourhood. An incision being made into this canal, it was found to terminate in a suppurating cavity, in which, lying quite loose, was a small bundle of hair. Radiating from this cavity were two canals leading to the abscesses in the nates mentioned above.

"It would seem probable that originally the hair was contained in a cyst, which, from the irritation caused by sitting, had suppurated, and the pus had burrowed in different directions."

In 1880 when Hodges wrote his classical description and suggested the most popular name for this condition there had already been a number of cases reported in the literature, although the condition was not generally recognized even by surgeons. In 1892 Mallory[4] reported 19 cases collected from the literature. That these cases did not represent the total number reported up to the time of publication is evident from the omission of the cases of Beall,[5] Mason,[6] Wendelstadt,[7] and others, nor did Mallory regard his report as complete, as he stated that he "appended a limited number of cases" to illustrate the main points of his paper. We are led to assume that by 1892 the condition was moderately well recognized by surgeons generally. The consensus of opinion in regard to treatment was that the cyst should be laid open, the contents removed, and the cyst wall curetted or excised.

The early discussions of the etiology of pilonidal sinus, like those current today, accepted the congenital nature of the lesion. Hodges[1] felt that the condition was caused by loose hair lodging in the post-anal dimple but offered no explanation of this defect except that it was congenital. Warren explained the condition on the basis that a hair follicle in the sacrococcygeal region became reversed, the hair growing inwards and continuing to grow drew the hole in after it by invagination. Aside from these novel explanations the chief theories as to the formation of pilonidal sinus are (1) a failure of the two halves of the body to unite; (2) failure of the medullary canal to become obliterated over the sacrum; (3) invagination of ectodermal structures over the sacrum.

The statement that pilonidal sinuses are caused by the failure of the two halves of the body properly to unite is a general one and gives no detailed concept of the actual processes which are responsible. Since it is always found at or near the midline, this conclusion can be rather generally accepted if we agree that the condition arises on a developmental basis. This latter is quite universally accepted as true. Attempts to explain the nature of the aberration of development have been frequent. Mallory[4] made microscopic sections in the sacral region of 7 fetuses ranging in age from 3½ to 6 months and found a canal lined with epithelium in 6 which he interpreted as remnants of the neural canal. He felt that in these remnants of the neural canal lay the source of pilonidal sinuses. He was not alone in this belief at that time, as he quotes Hermann and Tourneux[8] as holding the same view. Recently Weeder[9] has adopted this theory. Lannelongue[10] explains

the origin of the condition as due to the fact that the mesoblast is lacking particularly over the sacrum, the skin coming to lie close to the sacrum, and at places being bound to the bone. When subcutaneous tissue forms, these places where the skin is bound tightly to the sacrum forms dimpling, and if the depression is narrow enough may cause a sinus. A similar view was indicated by Stone[11] in his first paper on the subject. Later he indicated[12] that the condition was the result of a vestigial structure analogous to the preen gland in birds. A plausible explanation of the condition is that given by Oehlecker,[13] who pointed out that the caudal ligament attaches to a thin, hairless area of skin over the lowermost end of the spinal column. Due to discrepancies in rate of growth between skin and spinal column, shortening of the caudal ligament, and the growth of connective tissue between the skin and coccyx, the skin is drawn inwards and upwards, forming a dimple or even a sinus, depending on the amount of invagination present. Since the caudal ligament attaches to the so-called bald spot, the hair found in the sinus is the result of hair follicles in the region of the caudal bald spot which likewise has been invaginated. The formation of cysts is explained as being due to the usual metabolic products of the skin, which tend to block the opening, causing the inflammatory changes so frequently seen. Fox[14] called attention to one discrepancy in Oehlecker's theory in that if the so-called bald spot comes to lie over the sacrum instead of over the coccyx, the caudal ligament should cause the sinus to point downward from the skin over the sacrum toward the coccyx, instead of upward, as is the usual case. Fox, following a study of embryos, concluded that a pilonidal sinus originated following the invagination of ectoderm which is usually present in the fetus, and occasionally persists into adult life.

A clear, incontrovertible concept of the formation of pilonidal sinus is not as yet at hand. It is difficult to state definitely whether the condition is due to faulty development of the lower end of the medullary canal or to invagination of skin. The latter seems most plausible to us despite the rare reports of infection of the spinal sac from pilonidal sinus (Ripley and Thompson[15] and Moise[16]), and the occurrence of cysts and sinuses of similar nature occurring anterior to the sacrum (Masson[17] and Lahey and Eckerson[18]).

The frequent occurrence of postsacral dimple of the skin is an occurrence too common to be dismissed lightly and it is difficult to correlate these dimples of small or large size with medullary remnants. Markoe and Schley[19] report 89 dimples (29.1%) and 11 fistulæ (3.7%) in 300 consecutive births, while other figures given have ranged from 4% in adults to 39% in children. During physical examination made by one of us (C. G. J.) of 1040 men at a Citizens' Military Training Camp, 37 (3.6%) were found to have marked postsacral dimples or pilonidal sinuses. The majority of these individuals was under 21 years of age, and none was younger than 15.

Gross and histologic examination of sinuses removed at operation, even though infection has been present, likewise suggest that the sinus is of ectodermal origin. Descriptions of the examination of tissue removed has been reported by Newell[20] and by Fox.[14] The sinus is usually a branching or arborescent cavity, and apparently because of previous inflammation the lining consists largely of granulation tissue.

Hair may or may not be found in the cavity, usually lying free, rarely it is attached to the wall at the site of a hair follicle. True skin is commonly found lining some portion of the canal, fully developed sweat glands and hair follicles being present.

The history that one obtains from patients who are found to have a pilonidal sinus is usually clear enough to make the diagnosis, and this in addition to the physical examination should make the diagnosis easy. The patient is usually of early adult age, and complains of a discharge from the end of the spine. Usually the patient definitely states that the discharge is not from, but above the rectum and is sufficient to stain the clothing only occasionally. Many patients give the history that after discharging for some time the discharge stopped and a sore swelling developed over the sacrum. Following incision or spontaneous discharge of pus the wound healed slowly, only at a later date to have the swelling and tenderness recur. This cycle is often repeated many times until the diagnosis of pilonidal sinus is made by someone familiar with the condition. On physical examination a small dimple may be noted just above the tip of the coccyx. This dimple may be small enough to be represented by a small pin-point area, or it may be 0.5 cm. in diameter. If the opening is large enough to admit a probe, the instrument will usually pass upwards and towards the sacrum. A small drop of white or purulent fluid may be found at the opening. This material is usually increased in amount if gentle pressure is made over the sacrum.

In those patients who have suffered the mass to be incised, or who have had abscess formation with spontaneous rupture, one or more thick, wide scars may be seen over the sacrum, usually at a distance from the opening or dimple over the coccyx. These scars may be seen high over the sacrum or even on the buttocks, but usually they are found to lie over the middle of the sacrum. The majority of the sinuses contain hair, and if they have undergone abscess formation and are found open, hair may be found in the wound. In some cases there is no evidence of hair present and there is no history of any having been found at any previous time.

Of the first cases reported by Warren, 2 were females and 1 male. However, when one looks over the case reports in modern literature the proportion of females to males is low. In a series of cases operated upon on our service at the Hospital of the University of Pennsylvania there were 44 males and only 9 females. The proportion of females to males in the cases reported by Cattell and Stoller,[21] Glenn,[22] Stone,[11] Rogers,[23] Ferguson,[24] Owen,[25] Giffin and Archibald[26] and Masson[17] were about 1 to 4 (505 cases; 407 males and 98 females). In all these series there was a marked preponderance of males. Newell[20] has reported 11 cases all in females. It is possible that this preponderance of females may be accounted for by the source of Newell's clinical material. A distorted picture of the sex distribution of pilonidal sinus might be obtained should the cases be reported from a gynecologic clinic.

Newell's[20] cases ranged from 20 to 37 years of age. Most of the cases reported in the literature were found to be in early adult life. Our oldest case was 58 years old, the youngest 1½ years. It is to be remembered that age distribution of pilonidal sinus which comes to operation and those present but which are dormant are very likely

quite different. The surgeon seldom sees these cases unless infection has ensued, and usually does not see them until after the patient has had several incisions made by the general practitioner. In this regard Stone[11] and Ottenheimer[27] suggest the excision of symptomless and uninflamed pilonidal sinuses as a prophylactic measure. The difficulty in accepting this as a principle is that it is not only hard to determine which cases will have later trouble, but the identification of the condition is not easy until the sinus becomes dilated with its contents. A postsacral dimple in a child is hardly an indication that there is a sinus present. Nevertheless, should a sinus be found and well outlined there is little question but that it could be removed more safely and surely before inflammation has occurred than after.

The treatment of pilonidal sinus has varied from simple incision and curettage, as in the days of Warren, to radical excision as practised at the present time. For a time block excision of the sinus tract was the common method of treatment, in most cases the large defect resulting being packed open and allowed to granulate. This method requires prolonged dressing care and the end results are not always of the best. Lahey[28] called attention to the fact that the thick scar resulted in pain on sitting which caused considerable annoyance. Wide dissection of the sinus does not always give a good result, as even by this method of treatment recurrences occur. Lahey thought to replace the tissue removed from over the sacrum with a pad of fat drawn from over one buttock. The large defect would then lie over soft tissue and obviate the hard scar over the sacrum. This method of closure, while decreasing the scar over the sacrum, does not obviate the large defect which requires a long period of dressing.

The ideal method of treating pilonidal sinuses is that of complete excision of the tract after the injection of a suitable substance in the sinus to outline the tract, with primary closure. In order that an excision be successful the entire sinus tract must be removed. Small portions of the sinus left behind tend to cause a recurrence, and unless the sinus is well outlined it is quite easy to leave the remnants behind. In our own experience methylene blue to which hydrogen peroxid has been added as suggested by Stone[11] serves this purpose well. Melted paraffin may be used as suggested by Newell[20] for injection. The paraffin hardening tends to keep the sinus dilated during dissection, facilitating complete removal. If this method is used the injection must be made under enough pressure to insure complete filling, and the paraffin must not be allowed to cool before the small branches are reached.

We prefer, when possible, to dissect the sac out completely, with the sinus always under view and for this reason prefer not to resort to block excision. This method requires a little more time than block excision but there is no needless sacrifice of postsacral tissue.

When we are sure that the sinus is entirely removed, the wound is closed tightly. Silkworm gut stay sutures are placed in the depths of the wound on either side and brought out through the skin on the opposite side where they are tied over a gauze roll or lead wire to provide snug approximation and obliterate dead space. This method of closure is somewhat similar to that described by Colp,[29] except we have only occasionally had to resort to undermining of the skin flap

to obliterate dead space. The skin edges are approximated when necessary by silk or dermal sutures. In the depths of the wound only a minimum of catgut is used to control hemorrhage. In the majority of cases pressure applied over the bleeding points for a short time is sufficient to control all bleeding. We have had no difficulty with postoperative hemorrhage in the closed cases.

Following operation a snug dressing is applied and not disturbed for 5 days unless the patient's general reaction suggests trouble with the wound. The patient is kept in bed from 5 to 7 days.

For anesthesia we prefer spinal or local when possible. We do not feel that there is a tendency to spread infection by the use of local anesthesia since we attempt to infiltrate about and not through the operative site. We do not attempt operation on acutely inflamed sinuses but prefer to allow any redness or local heat to disappear before attempting removal.

Occasionally the sinus is too large to permit of primary closure throughout. Our policy is to treat these by partial closure with drainage. If none of the tissues about the area can be easily approximated the wound is packed open and the wound is allowed to granulate from the bottom. Rarely is it possible to suture these wounds secondarily.

Ferguson[24] advises the excision of pilonidal sinuses with primary closure. His results are excellent. We do not, however, feel that these patients should be permitted to get up after operation, as suggested by Ferguson. The wound should be allowed to heal before the patient is permitted ambulatory exercise. Not all wounds closed primarily will remain closed. The patient should be watched for infection in the wound, and when it is present the wound should be opened and packed. The treatment in this event is similar to that of a wound which is packed open primarily. Under this régime an attempt has been made to shorten the patient's convalescence and provide him with a wound which has the minimum of scar. If, however, the attempt at primary closure is not successful, the patient is no worse off than had the wound been packed primarily.

The treatment of pilonidal sinus which we have discussed is that of simple postsacral sinuses. This type forms the vast majority of those found; those penetrating the sacrum as described by Weeder[9] are rare, as are those in which the sinus extends under the coccyx and lies anterior to the sacrum. Naturally, pilonidal sinuses found in these unusual locations require special treatment since they are not so easily accessible and require more extensive dissection.

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(Titles have been omitted for sake of brevity.)

OPHTHALMOLOGY

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RECURRENT HEMORRHAGES INTO THE RETINA AND VITREOUS.

The most characteristic cases of the syndrome of recurrent hemorrhages into the retina and vitreous are those occurring in young adults, usually males, between the ages of 18 and 30 (Eales' disease). Quite similar cases are seen at times in older patients, which should probably be taken into consideration in a general discussion of the nature of the process.

The clinical course and ophthalmoscopic appearances of cases of this type are generally well recognized, and the major interest has centered in the study of the etiology and management of the disease. Clinically, the characteristic feature is the occurrence of repeated attacks of blurring of vision due to more or less massive hemorrhages into the retina and usually simultaneously into the vitreous of one or both eyes. Ophthalmoscopically, at the onset of an attack it is often impossible to see the details of the retina because of the clouding of the vitreous

by the hemorrhagic extravasation. In the interim between attacks, after the vitreous has cleared, which it usually does more or less spontaneously at least in early episodes, it is possible to see that the source of the bleeding is a lesion of one or more of the retinal veins. This lesion usually is characterized by a localized perivenous infiltration, often associated with marked irregularity in caliber and localized dilatations of the veins, and at times with obliteration of small venous branches later followed by the proliferation of new vessels into the retina and vitreous (retinitis proliferans). At times, foci of choroidal inflammation are seen, usually in the stage of atrophy and scarring; but it is doubtful if these can be considered to be the source of the hemorrhage. Damage to the arterial walls is also visible at times; but again the arterial lesions are probably of secondary origin. It seems most likely that a disease of the walls of the retinal veins is the primary lesion in all cases of recurrent hemorrhages into the retina and vitreous (Leber[1]). The outcome of many of these cases is more favorable than would be thought possible from the ophthalmoscopic appearances in the active phases of the disease. Some, however, terminate in detachment of the retina as the end result of the proliferation of vessels and scar tissue in the retina and vitreous, and in some the blood clots in the vitreous are never satisfactorily absorbed.

The etiology of these cases has remained rather obscure, even up to the present time. Numerous rather vague causes were assigned by most of the earlier authors: constipation, vicarious epistaxis, hemophilia, oxaluria, phosphaturia, gout, hyperthyroidism and other endocrine disturbances. Zentmayer[2] particularly favors some adrenal dysfunction as the underlying factor. Since it was first suggested by Noll[3] in 1908 that tuberculous lesions of the retinal veins were responsible, the belief in the probable tuberculous etiology of recurrent hemorrhages into the retina and vitreous has grown rapidly in favor. In 1921, Finnoff[4] listed 108 reported cases. In this series, the etiology given was syphilis, 5; constipation, 8; focal infection, 4; menstrual disturbances, 2; disturbances of the blood and circulation, 3; tuberculosis, 35, and cause undetermined, 51. Of the 5 cases reported by Finnoff himself, 3 were thought to be due to tuberculosis and 2 to focal infection.

In 1929, Young[5] reported 3 cases of recurrent hemorrhages into the retina and vitreous. One patient also had pulmonary tuberculosis. In the other 2 a low blood calcium was found: 6.5 mg. per 100 cc. in the first case and 9.5 mg. per 100 cc. in the second case. Calcium therapy apparently controlled the hemorrhages in the first case. Young analyzed the etiology of the cases reported up to the date of his paper. He found the causes listed as gastro-intestinal in 9, syphilis in 6, menstrual disturbance in 3, hyperthyroidism, hypertension and renal insufficiency in 4, focal infection in 10, tuberculosis in 76, and undetermined in 68.

Because of the fact that the syndrome of recurrent hemorrhage into the retina and vitreous is only rarely seen in association with clinical tuberculosis in other parts of the body, the diagnosis of tuberculosis in these cases must rest essentially on the patient's sensitivity to tuberculin. By some oculists the presence of a positive skin reaction to tuberculin is considered to be sufficient proof of the tuberculous nature of the ocular lesion. Most clinicians are not willing to accept such a

reaction as positive proof. Finnoff believed that the occurrence of a focal reaction in the eye after administration of tuberculin was necessary to establish the tuberculous etiology. It is rather dangerous in many of these cases to run the risk of a focal reaction in the eye, so that the diagnosis of tuberculous periphlebitis as the source of the hemorrhages is often difficult to establish, except presumptively.

Histologic examinations are seldom obtained in cases of this type, so that the actual anatomic nature of the local lesions has been difficult to demonstrate. In 1914, Fleischer[6] reported the histologic examination of a case of recurrent hemorrhages into the vitreous in which the eye was removed because of secondary glaucoma. He found a widespread tuberculous periphlebitis and endophlebitis of the retinal veins, characterized by a proliferation of endothelial cells and giant cells. Tubercle bacilli could not be found. It should be noted that the patient in this case had pulmonary tuberculosis.

In more recent years, the causative influence of focal infections in these cases of recurrent hemorrhages into the vitreous has received considerable support. This etiologic diagnosis lacks positive proof, since it must be based simply on the apparent response to the removal of foci of infection. Benedict[7] was unwilling to accept the focal infective origin in his cases since he could not reproduce the disease in rabbits by the injection of streptococci isolated from the foci of infection. In 1927, Godwin[8] reported a case which showed no response to tuberculin therapy but which cleared up after a radical operation on the frontal sinus. In 1934, Swab[9] reported 5 cases. He considered 3 of these to be due to tuberculosis and 2 to streptococcic focal infection. One of his cases had had pulmonary tuberculosis. In 1, the diagnosis of tuberculosis was based on the occurrence of focal reactions in the eye on the administration of tuberculin. In the third case considered to be tuberculous, the Mantoux test was positive and the disease responded favorably to the administration of tuberculin after the removal of foci and autogenous vaccine therapy had failed to influence its course. In 1 of these cases, the source of the hemorrhages was apparently an arterial instead of the usual venous lesion. The 2 cases considered to be of streptococcic origin responded favorably to the removal of infected teeth and the administration of autogenous vaccine. Tuberculin tests were negative in these 2 cases. Swab thinks that retinitis proliferans is a frequent sequel in the tuberculous cases but not in the ones associated with focal infection.

Recurrent hemorrhages into the vitreous occur in a certain number of patients with diabetes mellitus. The localized lesions in the retinal veins which are the source of the hemorrhages are quite similar to, if not identical with, those seen in the recurrent hemorrhages of adolescents (Eales' disease), and *retinitis proliferans* is an almost constant sequel. The patients are older than most patients with recurrent hemorrhages of tuberculous or focal infective origin, but usually younger than those with the more ordinary types of diabetic retinitis. In the series of 1052 cases of diabetes recently reported by Wagener, Wilder and Dry,[10] recurrent hemorrhages into the retina and vitreous with retinitis proliferans occurred in 19 cases. Waite reports 31 cases of hemorrhage of this type associated with lesions of the veins among

2002 diabetics. He believes that "this group is derived from diabetic patients with cardiovascular-renal complications and with outspoken disease of the retinal vascular tree. The part played by diabetes alone in this group seems to be trivial." It seems probable that in these cases the possibility of a local retinal tuberculosis complicating the diabetes is at least worthy of consideration.

The treatment of these recurrent hemorrhages into the vitreous has always been rather unsatisfactory. Some cases progress to an unfavorable termination in spite of treatment; others do surprisingly well without treatment. Unquestioned healed lesions of the veins of the characteristic retinitis proliferans type are seen at times in patients who have been unaware of any previous trouble with the eyes. Consequently, it is often difficult to evaluate properly the effects of any particular treatment. Essentially, two lines of therapy are possible: first, direct treatment of the cause and, second, treatment directed toward the absorption of blood in the vitreous without reference to its systemic etiology. If the etiology of the disease can be fairly definitely determined, specific treatment can be used. Thus Finnoff,[4] Wilmer,[11] Knapp,[12] Swab[9] and others recommend the administration of tuberculin in the tuberculous cases. Proven syphilitic cases should, of course, be appropriately treated. Foci of infection should be removed, if present, and Swab recommends the administration of autogenous vaccine in these cases. In cases of undetermined etiology, calcium therapy, injections of whole blood and of gelatin and various other measures have been suggested for the control of the bleeding.

In the cases of proven or suspected tuberculous origin, some authors believe that tuberculin therapy is dangerous because of the risk of focal reactions in the eye with increased hemorrhages. They prefer, therefore, a non-specific type of treatment in these as well as in the cases of undetermined origin. This form of treatment is directed particularly toward the absorption of the blood in the retina and vitreous, and to the building up of the patient's general resistance as an aid to the always-present tendency to spontaneous healing of the local lesions in the veins. Potassium iodid was the earliest favored drug, but its effect on tuberculous lesions is questionable if not definitely harmful. In the discussion of Finnoff's paper in 1921, Benedict reported favorable results from the non-specific use of arsphenamin. More recently, at The Mayo Clinic, intravenous injections of gold sodium thiosulphate have been used with even more favorable results. As with arsphenamin, gold sodium thiosulphate was tried in cases of probable retinal tuberculosis because of its beneficial effect on tuberculous lesions of the skin. Whether it has a more specific action on tuberculous than on streptococcic phlebitis is difficult to say at the present time.

As noted by Waite,[13] the prognosis in the cases of recurrent hemorrhages into vitreous in diabetes is uniformly poor. No form of treatment has been seen to give satisfactory results. Almost all of these cases end ultimately in blindness from retinal detachment or from organization of the blood in the vitreous. I have seen one patient, however, who recovered apparently spontaneously without diabetic or other form of treatment.

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